Chinese herbal medicine for psoriasis: Evaluation of clinical evidence and investigation of the anti-psoriatic effects of specific Chinese medicinal herbs

A thesis submitted in fulfilment of the requirements of Degree of Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to quality for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

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Publications

Journal articles

1. Deng S*, May BH*, Zhang AL, Lu C, Xue CC. Phytotherapy in the management of psoriasis: a review of the efficacy and safety of oral interventions and the pharmacological actions of the main plants. *Archives of dermatological research*. Nov 20 2013; DOI 10.1007/s00403-013-1428-4. (IF in 2012=2.708, Q1 in Dermatology)

2. Deng S, May BH, Zhang AL, Lu C, Xue CC. Plant extracts for the topical management of psoriasis: A systematic review and meta-analysis. *British journal of dermatology*. 2013; 169: 769-82. (IF in 2012=3.759, Q1 in Dermatology)

3. Deng S, May BH, Zhang AL, Lu C, Xue CC. Topical herbal formulae in the management of psoriasis: systematic review with meta-analysis of clinical studies and investigation of the pharmacological actions of the main herbs. *Phytotherapy research: PTR*. Jul 1 2013; DOI 10.1002/ptr.5028. (IF in 2012=2.068, Q3 in Medicinal chemistry, Pharmaceutical & pharmacology)

4. Deng S, May BH, Zhang AL, Lu C, Xue CC. Topical herbal medicine combined with pharmacotherapy for psoriasis: a systematic review and meta-analysis. *Archives of dermatological research*. 2013; 305:179-89. (IF in 2012=2.708, Q1 in Dermatology)

5. May BH, Zhang AL, Zhou W, Lu CJ, Deng S, Xue CC. Oral herbal medicines for psoriasis: a review of clinical studies. *Chin J Integr Med*. 2012; 18: 172–178. (IF in 2012=1.059, Q3 in Integrative & complementary medicine)

6. Deng S, May BH, Zhang AL, Lu C, Xue CC. Herbal medicines in the topical management of psoriasis: a systematic review of clinical evidence. (Abstract for the 2nd EADC) *J. Dermatol.* 2012; 39: 226-227. (IF in 2012=1.765, Q2 in Dermatology).

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7. Deng S, May BH. RCT of acute psoriasis according to blood-type (*Xue feng*) syndrome differentiation. *Australian Journal of Acupuncture and Chinese Medicine*. 2012, 7: 35-36.

Conference presentations

8. Deng S, May BH, Zhang AL, Lu C, Xue CC. Evaluation of topical herbal medicine for psoriasis, by poster & oral presentation on *the 10th meeting of Consortium for Globalization of Chinese Medicine (CGCM)*, 26-28 August 2011, Shanghai.

9. Deng S, May BH, Zhang AL, Lu C, Xue CC. Herbal medicines in the topical management of psoriasis: a systematic review of clinical evidence, by poster presentation on *the 2nd Eastern Asia Dermatology Congress (EADC)*, 13-15 June 2012, Beijing.

10. Deng S, May BH, Zhang AL, Lu C, Xue CC. Herbal medicines in the topical management of psoriasis: a systematic review with meta-analysis of clinical evidence, by poster presentation on *ASMR Victorian Student Research Symposium*, 3 June 2013, Melbourne.

11. Deng S, May BH, Zhang AL, Lu C, Xue CC. Topical herbal medicine in anti-psoriatic therapy: clinical efficacy, safety and pharmaceutical actions, by oral presentation on *the 7th VACPS Research Symposium*, 2 November 2013, Melbourne.

* Equally contributed to the study

List of Abbreviations

For protein and drug target names see: Appendices 19 and 20

AEs: adverse events;

APP: anti-psoriatic pharmacotherapy;

BSA: body surface area involvement

BUN: blood urea nitrogen;

CAM: complementary and alternative medicine;

CD: circular dichroism;

CE: cornified envelope

CD4+ T cells: T-cell surface glycoprotein CD4;

CHM: Chinese herbal medicine;

CI: confidence interval;

CM: Chinese medicine;

DLQI: Dermatology Life Quality Index;

FDA: Food and Drug Administration;

FE: fixed effect model;

HaCaT: immortalized human keratinocytes cells;

HeLa cells: a cell from a sample taken from a woman called Henrietta Lacks and was named using the two initials of her first (He) and last (La) names;

HLA: human leukocyte antigen;

HM: herbal medicine;

MD: mean difference;

N.S.: not stated;

PASI: Psoriasis Area and Severity Index;

PDI: Psoriasis Disability Index;

PGA: Physician’s Global Assessment;

PsA: psoriatic arthritis;

PUVA: psoralen and ultraviolet A;

QLI: Quality of Life Index;

RevMan: Review Manager software;

RCT: randomized controlled trial;

RE: random effect model;

RR: relative risk;

PSD: preparation that is specific for the disease;

SMD: standardized mean difference;

TCM: traditional Chinese medicine;

TBI: total body surface area involvement;

THP1: human monocytic cell line;

TSD: Treatment based on syndrome differentiation;

UVB: Ultraviolet B;

WBC: white blood cell;

WM: Western medicine.

Summary

Psoriasis is a chronic and recurrent skin disease that affects 1-5% of the population in various countries. The cause of psoriasis is not fully understood but the disease is thought to be a T-cell mediated inflammatory disorder. Conventional medical treatments can control the symptoms associated with psoriasis but can have significant side effects. There is, as yet, no curative regimen for the clinical management of psoriasis. Around half of psoriasis patients use some forms of complementary and alternative medicine including herbal medicine (HM) used topically and orally. In China, Chinese HM is frequently used by psoriasis patients and may be prescribed by dermatologists in combination with pharmaceutical medicines.

A number of clinical trials of HMs for psoriasis have been conducted but many different HMs have been used and trials have been diverse in their design, duration and in the outcome measures used. Consequently, the clinical efficacy of these HMs has yet to be systematically evaluated.

The project aimed to evaluate the clinical efficacy and safety of HM for psoriasis, identify the herbs for which the clinical evidence is strongest, investigate the anti-psoriatic actions of the most promising herbs, and develop an *in silico* method for investigating the targets of these herbs.

The first component of the project was to systematically evaluate the clinical evidence using systematic reviews. This involved comprehensive searches of the literature followed by assessments of the quality of published clinical trials on psoriasis and meta-analyses of outcome measures to determine the best available clinical trial evidence. This component used the methods developed by the Cochrane collaboration and extended the methods used for meta-analysis to address the particular issues raised by the use of multi-ingredient formulations.

This first component was divided into two parts. The first part analysed clinical trials of HMs used internally and the second part included HMs used as topical preparations. Due to the

diversity in the use of topical HMs, the second part was further divided into three sections based on the type of topical HM intervention: single herb, multi-ingredient herbal formula, and HM plus anti-psoriatic pharmacotherapy (APP).

Based on the results of the systematic reviews and meta-analyses of 39 studies a short-list of 12 herbs was selected as showing promise for the internal and/or external treatment of psoriasis: *Oldenlandia diffusa*, *Rehmannia glutinosa*, *Salvia miltiorrhiza*, *Aloe vera*, *Indigo naturalis*, *Camptotheca acuminata*, *Mahonia aquifolium*, *Sophora flavescens*, *Lithospermum erythrorhizon*, *Cnidium monnieri*, *Dictamnus dasycarpus* and borneol.

The second component of the study focussed on the likely mechanisms of action of the herbs identified in the first component. It was possible that the actions identified were the result of single or multiple compounds contained in the herbs. Also, it was possible that the herbs acted on single or multiple targets. The investigation of how these herbs might act in the management of psoriasis involved a series of steps.

Firstly, for each of the main herbs, the *in vivo* and *in vitro* evidence for biological activity of relevance to psoriasis therapy was reviewed. This is evidence for anti-inflammatory, anti-proliferative, anti-angiogenic, wound healing/skin repair and/or anti-pruritic actions for extracts of the plants and/or their bioactive constituents.

In the second part, the compounds contained in the short-listed herbs and their associated species were identified using Encyclopaedia of TCM and other sources. This identified 482 compounds. The targets of these compounds were identified for each herb using the database HIT resulting in 350 biological targets.

The main therapeutic targets of relevance to anti-psoriatic therapy were identified using the DrugBank database to search for the targets of 20 drugs with known anti-psoriatic effects (APPs) that had received FDA approval for psoriasis. The search located 70 targets with known actions including Glucocorticoid receptor (NR3C1), Prostaglandin G/H synthase 1 & 2 (COX 1 & 2), Retinoic acid receptor (RAR) alpha, beta & gamma-1, RXR-alpha & RXR-beta, T-cell surface antigen CD2 (CD2), Tumor necrosis factor (TNF) and Vitamin D3

receptor (VDR).

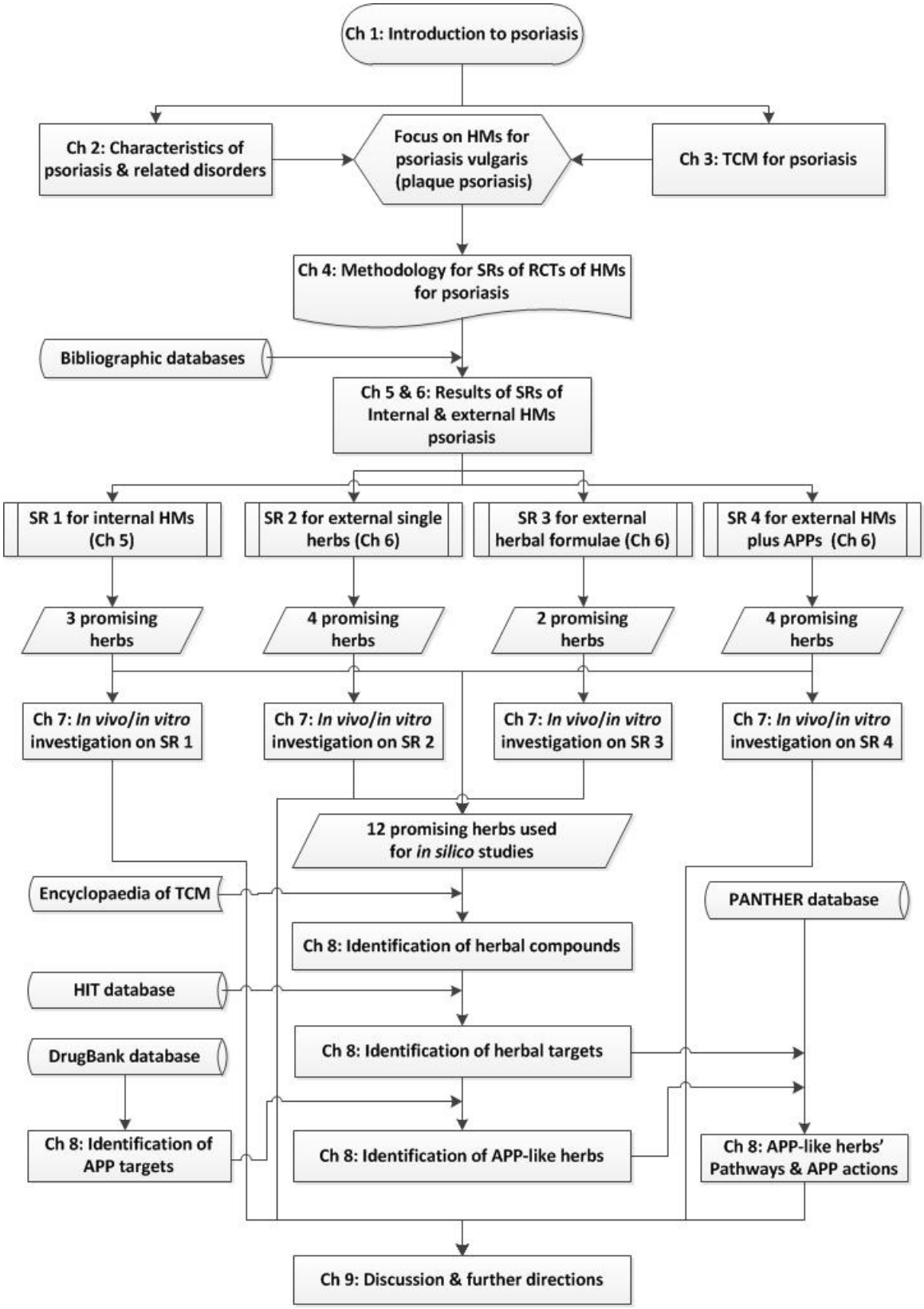
Next, the targets of each of the compounds contained in the short-listed herbs were filtered based on the targets of the APPs. Ten targets were common to the APPs and the herbs. This enabled the identification of 11 herbs which shared at least one target with at least one of the APPs. Since some of these targets were enzymes from the Cytochrome p450 family, these were filtered out leaving the 9 herbs as follows: Dan shen (*Salvia miltiorrhiza*, *S. sinica*), Di huang (*Rehmannia glutinosa*), Bai hua she she cao (*Oldenlandia diffusa*), Lu hui (*Aloe vera, A. ferox*), Qing dai (*Indigo naturalis*), Xi shu (*Camptotheca acuminata*), Gong lao mu (*Mahonia* spp), Ku shen (*Sophora flavescens*) and Zi cao (*Lithospermum erythrorhizon, Arnebia* spp). These were considered the herbs most likely to have APP-like actions.

Although these herbs had targets that were of known or likely relevance to psoriasis therapy, the herbs typically contained multiple compounds and some of the targets of these compounds which were not known targets of the APPs may also be of relevance to psoriasis. In order to explore how the multiple compounds in the herbs might be affecting biological processes, the database PANTHER was used to identify which biological processes and which pathways could be involved in the actions of these herbs.

Since it was impractical to analyse all the 350 targets of the HMs, the following four herbs were selected for analysis using PANTHER: Dan shen, Di huang, Qing dai and Xi shu.

Each herb had targets that were involved in between 48 and 59 pathways. The main pathways in which these targets were involved were identified as: Apoptosis signalling pathway, Angiogenesis, Gonadotropin releasing hormone receptor pathway, Inflammation mediated by chemokine and cytokine signalling pathway, and Interleukin signalling pathway. These pathways are primarily related to inflammation, proliferation and angiogenesis.

The approach used in the second component was proposed as a more general method for adding value to the results of systematic reviews of herbal medicines and as an approach to identifying directions for clinical trials and drug discovery. The limitations of this approach and the implications for further research were discussed.



Ch: Chapter, HM: Herbal Medicine, SR: Systematic Review, APP: Anti-psoriatic pharmacotherapy, RCT: Randomized Clinical Trial, TCM: Traditional Chinese Medicine

Fig. S.1 Flowchart of study progression and thesis content

Chapter 1: Introduction

This chapter describes the types and features of psoriasis as well as discusses the epidemiology and economic impact of this disease. A brief review of the literature on the clinical management of psoriasis available at the time of writing is also provided. The chapter concludes with a statement of the aims of this study and specific research questions.

1.1 Overview of the disease

Psoriasis is a chronic inflammatory disease characterised by clearly delimited erythaematous plaques with large silvery scales and/or mild itching. It is often accompanied by 'Auspitz sign' (expanded blood vessels underneath the plaque), 'tache de bougie' (waxy appearance induced by scratching the involved skin) or Koebner phenomenon (psoriasis at the site of scars and minor skin injuries). Furthermore, 5%–10% of psoriasis patients have psoriatic arthritis (PsA), which mainly affects the distal interphalangeal joints and metacarpophalangeal joints (1).

Psoriasis presentation patterns vary in appearance and location. The common types are plaque psoriasis, guttate psoriasis, scalp psoriasis, nail psoriasis, flexural psoriasis and psoriasis of palms and soles. Less common patterns include napkin psoriasis in infants, acute generalised pustular psoriasis and erythrodermic psoriasis. The plaque pattern (psoriasis vulgaris) is the most common type (2).

Psoriasis is also categorised as Type 1 or Type 2 depending on the type of human leukocyte antigen (HLA) present. Type 1 is characterised by early onset and mostly affects the skin, whereas Type 2 usually appears at later stages in life and can affect the nails and joints (3).

Till date, there is no uniform therapeutic regimen for the clinical management of psoriasis (4) despite the existence of several guidelines developed by various institutions that have been recommended by the relevant authorities (2, 5). The treatment of psoriasis and management of psoriasis patients varies widely throughout the world (6).

Research on inflammatory mechanisms of psoriasis at the genetic, molecular and cellular levels, undertaken over the last 20 years, has improved our understanding of this disease. New treatments have been developed and have markedly improved the clinical efficacy of psoriasis management (4). Current conventional approaches include a range of topical medications, phototherapy and systemic therapies using pharmaceutical and biological agents (2, 7). Nevertheless, there is no single effective treatment for psoriasis; more research and development are required to improve the efficacy and safety of future therapies for psoriasis.

1.2 Epidemiology of psoriasis

1.2.1 Incidence

Studies have investigated the incidence of psoriasis in specific populations; however, there are no definitive data on its global incidence (8-10).

The first study on the incidence of psoriasis was conducted in Olmstead County Minnesota, USA during 1980–1983. The study used medical records of the local population and involved 132 newly diagnosed psoriasis patients. The overall average annual incidence rate was 57.6 per 100,000 person-years (54.4 per 100,000 person-years for males and 60.2 per 100,000 person-years for females). The overall rate of incidence peaked in the 60–69-year age group at 112.6 per 100,000 person-years. For females, the rate increased until 69 years of age, whereas for males, the rate increased with age. Because 58% of subjects were categorised as mild (<10% body surface area), they may not have considered the condition to be severe enough to visit their doctors; therefore, the real incidence of psoriasis may have been underestimated (8).

In 1998, a survey involving 8,045 Norwegian twins aged 19–31 years (4,602 females and 3,443 males) found that the incidence rates peaked in the 24–27-year age group for males and in the 16–19-year age group for females. The rates were 300 per 100,000 person-years for males and 290 for females. The mean age at the onset of the disease was much lower for females (14.8 years) than for males (17.3 years). The study also showed a definite linear

increase in incidence rates, although they peaked at different age intervals: the mid-twenties for males and late teens for females (10).

The incidence rates are very different in the 2 abovementioned studies. This could be attributed to differences in methodology and populations. The Minnesota study was limited to patients diagnosed with psoriasis at a hospital clinic, whereas the Norwegian study used a population-based method. In the first study, mild cases may have been omitted and the incidence of psoriasis could have been underestimated. The populations studied were also considerably different. The Norwegian study was limited to twins aged 19–31 years with Type 1 psoriasis, whereas the Minnesota study included all psoriasis types and all ages (8, 10).

1.2.2 Prevalence in the world, Australia and China

Psoriasis is found throughout the world; however, there is a wide variation in its reported prevalence. The prevalence of psoriasis in the US is estimated to be approximately 2% (3). However, only a few epidemiological studies of psoriasis have been population-based, and almost all data have been derived from references to other types of studies (11). Because patient ethnicity may affect the prevalence of psoriasis, studies that do not use population-based methods can produce biased results, can differ between countries, regions and areas and the validity of the findings might be limited. For psoriasis, population-based factors are as significant as genetic and environmental factors. However, it is also important to differentiate between various subpopulations and their individual healthcare needs (12).

The factors that affect the reported prevalence include the country investigated, definition of prevalence (point, period or lifetime), sampling method and methods used to diagnose the disease (e.g. disease reported by a patient with/without confirmation by a practitioner) (12). Among the abovementioned factors, the definition of prevalence should be clarified first. It is ‘the proportion of individuals in the population who have the disease of interest in a specified time period’ (p 1538), and it could refer to the lifetime prevalence of the disease (13).

Some studies conducted using appropriate approaches that allowed making reasonable inferences have been the subject of a recent review. Cimmino (2007) estimated the average global prevalence of psoriasis to be 3%–4%, without evident differences between the genders. Furthermore, Cimmino estimated that the prevalence of PsA should be 0.5%–1%; this estimate is based on the fact that although the percentage of psoriasis is 3%, approximately 15%–30% of the patients also have PsA. The prevalence of psoriasis is probably underestimated because the disease is mainly reported by patients themselves. This approach may miss undiagnosed mild psoriasis, and the lack of precise classification criteria and the elusive nature of skin diseases in general may result in the disease being undiagnosed (14). For example, the National Health and Nutrition Examination Survey (NHANES) 2003–2004 in USA showed that the prevalence of undiagnosed active psoriasis, based on a conservative definition and a broader definition, was 0.4% and 2.28%, respectively, of the US population aged 20–59 years. These percentages accounted for approximately 600,000 and 3.6 million US adults, respectively. These results are almost comparable with the number of adults diagnosed with psoriasis during the same period (over 5 million; prevalence of 3.15%) (15).

In a review of the prevalence of psoriasis in different countries and populations, Cimmino (14) reports a large variation. However, few of the epidemiological studies reviewed were population based, and there was a considerable variation in the methods used. The prevalence of psoriasis varied from 0% in the Samoan Islands to 11.8% in Kasach'ye on the Arctic Circle (16). Mali and Nigeria had a low prevalence of psoriasis (0.05% and 0.08%–0.4%, respectively). In addition, Angola had a low prevalence (0.3%). East Africa had 0.7% prevalence, which was the same level as that in the African–American population in the USA. However, higher prevalence rates were found in Uganda (2.8%), Tanzania (3%) and Kenya (3.5%), with the highest rate being found in South Africa (4.5%).

The prevalence of psoriasis in India has been estimated to be 0.7%, whereas that in Malaysia has reached 4%–5.5%. Approximately 0.3%–1.2% of the Japanese population was affected by the condition; however, its prevalence in the Henan Province of China was only 0.4%.

The only data available for the Middle East were for Kuwait; the prevalence rate was 3.1%, it was similar to that in Egypt (3%).

In Europe, the prevalence of psoriasis in Norway, Croatia, UK and Former USSR was low at 1.45%, 1.55%, 1.6% and 2%, respectively. The prevalence of psoriasis in Spain was high at 3.7%, and even higher rates were found in Scotland (4.8%) and Ireland (5.5%). The highest rate in Europe was found in Germany (6.5%) (14).

Data for America showed the lowest prevalence rate in Brazil (1.3%), followed by Venezuela (2%), and the highest prevalence rate in the Caribbean (6.5%). Approximately 4.6% of the population of the USA was affected by psoriasis, while 4.2% prevalence was found among Paraguayans and 4.7% among Canadians. Interestingly, the prevalence in some countries showed a large variation depending on the origin of the population. For instance, the prevalence among Caucasians in Australia was 2.6%, whereas that among the aboriginals was 0%. Similarly, the overall prevalence in the USA was 4.6%; however it was only 0.7% in African Americans and 0% in Native Americans and Alaskan natives. In general, it seems that psoriasis tends to occur at higher rates in Europe and among white populations (14).

The Australian prevalence of psoriasis has been estimated to be 2.6% (14). According to Psoriasis Australia, there are approximately 350,000 Australian patients with plaque psoriasis, and 10% of these can be categorised as cases of severe chronic plaque psoriasis (17). An epidemiological study of skin conditions, including psoriasis, using a random population-based survey method was implemented from August 1997 to February 1998 in central Victoria, Australia. The study found a 6.6% [95% confidence interval (CI), 5.4%–7.9%] prevalence that varied with age and sex (18). The rate for males differed from that for females; it was 8.9% (95% CI, 6.8%–11.0%) versus 4.5% (95% CI, 3.2%–6.3%), giving a gender rate ratio of 2.0 (95% CI, 1.3–3.2) However, the study found that the prevalence of psoriasis was not likely to be related to age. The percentages of individuals suffering from mild, moderate and severe psoriasis were 81.1%, 16.1% and 2.8%, respectively; however, the severity was not associated with sex or age. Only 41 of the 99 respondents who were found to have psoriasis mentioned psoriasis in their disease history questionnaire. The

authors believe that the the current prevalence rate may be higher than the previously reported rate because of the use of a specialist clinician, which resulted in greater sensitivity in detecting the disease. When the authors removed 80% of cases classified as mild, the prevalence fell to 1.8% in males and 0.6% in females, which was closer to the earlier estimates of prevalence rates. However, this also resulted in a higher male-to-female prevalence ratio of 3.0 (18).

From 1976 to 2008, a series of surveys on psoriatic prevalence were conducted in China. They are listed in Table 1.1 in chronological order (19-24).

Table 1.1 Prevalence Surveys of Psoriasis in China

Year	**Area**	**Method**	**Prevalence (%)**	**Sample Size (n)**
1976–1977	Xinjiang autonomous region	Not stated	0.18%	18,498
1984	23 provinces & municipalities	Clue filtering	0.12%	5,742,066
1987	Inner Mongolia autonomous region	Clue filtering	0.22%	108,975
1993–1994	Xuzhou Prefecture-level city, Jiangsu Province	Stratified & overall random sampling and single blinding	0.11%	98,642
2001	Suzhou Prefecture, Anhui Province	Stratified & overall random sampling	0.11%	92,857
2008	6 provinces & municipalities	Overall sampling	0.47%	17,345

The survey of 23 provinces and municipalities (21) conducted in 1984 by the National Survey Group of Psoriasis Prevalence was the most comprehensive. It was the largest and the most extensive survey in the field of epidemiology of psoriasis in China; it sampled 6,617,917 people, covering 53 sites in 24 provinces and municipalities, and recorded data for 5,742,066 respondents at 49 sites in 23 provinces and municipalities. Apart from a 0.12% general prevalence rate of psoriasis, the study also found other significant differences in prevalence, as described below.

a) Difference between the northern and southern regions: With a latitude of 35 degrees north as the boundary, the standardised prevalence rate was 0.200% in 12 northern cities versus 0.140% in 14 southern cities and 0.180% in 6 northern villages versus 0.065% in 14 southern villages. In particular, the highest rates were 0.439% in Dehui County, the Jilin Province in northeast China, and 0.442% in the Capital Steel Corporation in Beijing, while the lowest rate was 0.006%–0.008% in the Guangdong Province, southern China.

b) Differences between urban and rural areas: The prevalence rate was 0.176% in the former and 0.100% in the latter. This was also evident in similar geographical environments. For instance, it was 0.259%, 0.141% and 0.082% in Nanjing, a highly industrialised municipality; Taizhou, a small city and a village in Yangzhou, respectively.

c) Differences between males and females: The corresponding rates were 0.168% versus 0.124%. In addition, the study revealed that the patients of aged 20–54 years constituted 78% of the total patients; young and middle-aged adults formed the largest group of psoriasis sufferers. In total, 75% of patients had their first occurrence by the age of 34 years. The most frequent onset age bracket for males was 20–24 years (17.22%), whereas that for females was 15–19 years (18.46%). The survey revealed that most patients were diagnosed with psoriasis vulgaris (97.9%) and the remaining patients had psoriasis of the erythrodermic (0.58%), pustular (0.69%), erythaema (0.04%) or arthritic type (0.69%). The majority of patients were classified as mild psoriasis sufferers (62.81%), whereas moderate and severe groups constituted 29.47% and 7.71% of the total, respectively. The study also showed a remarkable positive association with family history (32%).

1.3 The cost of prevention & treatment

The economic burden (25) for psoriasis patients includes a wide range of aspects such as medical visits and prescriptions, hospitalisation, medication costs and over-the-counter (OTC) products for skin care. It can also include additional therapies, travel expenses, loss of work and a negative effect on professional opportunities because of the long-term duration of the disease. The disease also affects the overall healthcare budget. Therefore, we should evaluate

the relevant expenses involved in the management and treatment of psoriasis. In general, the costs of the disease can be divided into 3 types:

a) **Direct costs**: the direct expense of the therapy;
b) **Indirect costs**: the investment from a societal point of view and
c) **Intangible costs**: the burden to patients and their families, which may not be easy to estimate.

1.3.1 Total cost of psoriasis management

The total cost of psoriasis management, particularly in cases of moderate-to-severe psoriasis, usually treated with phototherapy or systemic agents (26), arises from a series of expenditures throughout the consultation, examination, diagnosis and treatment that a patient with psoriasis may undergo (and may be reimbursed by a third-party), for example:

a) **Office visit**: level 3 return, nursing visit;
b) **Laboratory work**: complete blood count, complete blood count with differential, liver function test, lipid panel, basic metabolic profile, complete metabolic profile, magnesium, T-cell CD4 count, tuberculosis PPD;
c) **Radiological studies**: chest X-ray;
d) **Procedures**: liver biopsy;
e) **Infusion**: 1-h or >1-h infusion and
f) **Treatment**: ultraviolet B (UVB), psoralen and ultraviolet A (PUVA).

In addition, the drug acquisition costs can be estimated on the basis of their average wholesale price.

In the USA, the direct costs of adult psoriasis (including PsA) were studied in 1997 (27). The study revealed that the main direct medical costs were hospitalisation, inpatient physician services, outpatient physician visits and prescription medications. In addition, OTC costs were estimated by referring to the changes in the number of psoriasis patients, the consumer price index (CPI) and the OTC drug index [series SEMB – Non-prescription Drugs and

Medical Supplies (28)]. Because certain expenses such as emergency department services, diagnostic radiology and laboratory services and nursing home or home healthcare services were weighted lower, they were not included in the analysis. The study revealed that the total direct medical expenses for approximately 1.4 million psoriasis patients were US$ 649.6 million (M) per year. This included hospitalisations ($ 30.5 M); outpatient physician visits ($ 86.6 M); photochemotherapy ($ 27.4 M); dermatological prescription drugs ($ 147.9 M) and OTC drugs ($ 357.2 M). The authors noted that the overall cost was smaller lesser than that in a 1979 study; they attributed this to a fall in the hospitalisation rate since 1979 and differences in the methods used to cost medical services.

For patients with moderate-to-severe chronic psoriasis vulgaris, a study (29) has been conducted in 17 centres in Germany to determine the mean annual cost and expenditure and cost per flare in out-patients and office-based care. The data were obtained from 192 of 227 enrolled patients and consisted of direct costs to patient and from third-party payers (TPP) and indirect costs from the patient. In general, the cost per patient was €2,866 (including €864 reimbursed by a TPP and €1,440 of indirect costs) per year. However, for systemic therapy, the total cost rose to €4,985, compared with €1,173 for topical and/or phototherapy.

In 2002, Jenner et al. published the first longitudinal study of morbidity and cost of psoriasis (30). This was a prospective cohort study conducted in Melbourne, Australia from 1997 to 1999. It included an initial interview and 8 subsequent 3-monthly follow-ups. Complete diary data were provided by 46 of 83 originally recruited participants. This included the cost of medical products (i.e. prescription medications, OTC treatments and household items) and costs of medical consultations, including (a) cost of consultation with a bulk-billing general practitioner, (b) cost of consultation with a general practitioner paid by the participant, (c) out-of-pocket cost for specialist fees and (d) cost of photochemotherapy with PUVA and UVB. The study reported that the average annual cost of psoriasis products for each participant was AUD$ 254.25; however, the individual cost over the 2-year period could vary from zero for a mild psoriasis patient to AUD$ 2000 for a severe psoriasis patient. In fact, the average OTC product cost was more than the average out-of-pocket cost for

prescription products. Medical consultation costs ranged from AUD$ 128 to approximately $ 1206 p.a., with a mean of AUD$ 473. In addition, there was an average of AUD$ 185.28 in out-of-pocket costs in consultation fees to other healthcare providers. The authors noted that the use of Psoriasis Area and Severity Index (PASI) may not provide an accurate assessment of the severity of the disease over time and that patient's self-assessment may not agree with the dermatologist's assessment.

A Chinese study, conducted from March 2001 to October 2003 investigated the cost of long-term psoriasis therapy using a specific questionnaire (31). In total, 132 patients who had suffered from psoriasis for 10 or more years participated in the study. They were variously employed as labourers, agricultural workers, management staff, self-employed, and others. The total amounts spent by the respondents on their psoriasis treatment varied considerably, from RMB¥ 1000 to RMB¥ 150,000. The total long-term costs were categorised into 4 groups: ≤RMB¥ 5000; RMB¥ 5000–20,000; RMB¥ 20,000–50,000 and >RMB¥ 50,000.

Patients in different occupations reported significantly different costs of treatment; management staff and self-employed patients bore higher expenses than patients with other professions ($\chi^2 = 38.44$, $P < 0.01$). The total cost of treatment also varied with the severity of psoriasis (divided into 4 groups on the basis of the latest relapse); the differences were highly significant ($\chi^2 = 78.88$, $P < 0.01$). The individuals with a higher severity of psoriasis had spent more than those with a milder form of the disease. The majority of participants in cost-groups I and II (94% and 87.18%, respectively) had psoriasis of 'mild' to 'middle' severity. In cost-group IV (i.e. the highest expenditure), a large proportion of patients suffered from 'medium-severe' and 'severe' psoriasis (37.5% and 43.75%, respectively).

According to China Labour Statistical Yearbook 2004, the average annual wages of the office staff and manual workers were RMB¥ 9,774 and RMB¥ 11,001 for Manufacturing Industry in 2001 and 2002, respectively, and RMB¥ 12,142 and RMB¥ 13,975 for Government Agencies, Party Agencies & Social Organisations in 2001 and 2002, respectively (32). The cost of psoriasis treatment mainly fell into cost-groups I and II; the amounts spent were between 41.18% and 205.90% of the annual income in 2001 and

between 45.45% and 181.80% of the annual income in 2002.

1.3.2 Cost of specific interventions

1.3.2.1 Topical therapy

Because psoriasis is a persistent and progressive disease with a tendency to relapse after remissions, lifelong expenses accompany lifelong care (33). The first-line intervention for psoriasis is the use of topical agents, including steroids (i.e. fluocinonide), retinoids, calcipotriol (calcipotriene in US) and tazarotene. These remedies play substantial roles in the management of psoriasis. A US study investigated the cost-effectiveness of each topical therapy. In the study, pharmacoeconomic decision–analysis model was developed and validated. Data on the clinical efficacy (including clearance and relapse rates) of calcipotriol, tazarotene and fluocinonide were obtained from clinical trials and analysed via meta-analysis. The costs of medical consultation, treatment preparation, laboratory testing and treatment for potential side effects were taken into account in the decision model. The expected costs of a condition-free day were the basis of cost-effectiveness analysis. The study revealed that 0.1% tazarotene was 16.74% more cost-effective than 0.05% tazarotene, 143.75% more cost-effective than calcipotriol and 85.46% more cost-effective than fluocinonide. The anticipated expense of a condition-free day was $ 49.46 for 0.1% tazarotene, $ 57.74 for 0.05% tazarotene, $ 91.73 for fluocinonide and $ 120.56 for calcipotriene. The study recommended the use of tazarotene for patients with mild-to-moderate stable plaque psoriasis as the most cost-effective topical therapy.

1.3.2.2 Systemic, phototherapy and biological therapy

In 2003, Feldman analysed the annual cost of treatment for severe psoriasis with a focus on comparison between established systemic treatments and the newly introduced biological agents alefacept, etanercept and infliximab (26). The annual cost of treatment with methotrexate, UVB, PUVA, acitretin, cyclosporine, etanercept, alefacept or infliximab varied from US $ 3,600 to 34,600. Methotrexate treatment was the cheapest, at US$ 1,600 per year. The second lowest cost was for phototherapy, namely US$ 3,600 for UVB and

US$ 4,600 for PUVA. Cyclosporin was more expensive than acitretin at US$ 6,500–10,000 versus US$ 5,200 per annum. Alefacept, etanercept and infliximab were all considerably more expensive than the abovementioned interventions; however, the cost depended on the individual dose. For example, the cost of a 25 mg dose of etanercept twice a week (the standard dose also used in rheumatoid arthritis) was US$ 16,900, whereas that for a 50 mg dose was US$ 33,000. Similarly, the annual cost of alefacept treatment based on an average of 1.5 × 12-week courses was US$ 16 000–20 000, which included the cost of the drug, drug administration, laboratory testing and travel. However, the annual direct costs for alefacept, etanercept and infliximab were similar. In terms of cost per treatment success, the most expensive were etanercept (25 mg twice a week, US$ 35,900) and intravenous alefacept (US$ 40,600), followed by infliximab at 5 mg/kg (US$ 22,500). Methotrexate was the cheapest drug at US$ 5,400, while the costs of UVB (US$ 5,100) and PUVA (US$ 5,700) were comparable. Cyclosporin was considerably more costly at US$ 14,200, and acitretin monotherapy was the most expensive of the established treatments (US$ 17,300); however, acitretin is more commonly used in low doses in combination with phototherapy. The authors of the study concluded that UVB is one of the least costly and safest therapies but it is not very convenient. Although methotrexate is a cost-effective second-line treatment, its risks limit its long-term use. Similarly, skin cancer risks of PUVA therapy limit its long-term use. The new biologicals carry a lower risk-to-benefit ratio but have the disadvantage of a high cost.

1.4 Research background

The causes of psoriasis are still unclear, and the current conventional therapies are mainly used to control the symptoms and/or signs (34, 35). Although there have been some advances in psoriasis symptom management, the efficacy of the available treatments remains limited. The conventional treatments are also associated with significant side effects, including the various side effects of corticosteroids; skin cancer risks of PUVA; teratogenic effects of the oral retinoid acitretin; myelosuppression and liver fibrosis due to methotrexate; toxicity and gastrointestinal intolerance of fumaric acid; reactivation of latent tuberculosis, hepatotoxicity,

lymphoma and congestive heart failure due to the agents blocking T-cell activation and tumour necrosis factor (TNF)-α and renal damage caused by cyclosporine (35). These side effects limit the application of certain therapies, particularly in long-term treatment.

The costs of conventional psoriasis therapy are considerable, particularly for the new systemic drugs used during prolonged periods. The recalcitrant nature of this disease, the limitations of conventional therapies, their associated cost and the problems caused by their side effects are the issues that concern patients, dermatologists and government health agencies. It is necessary to seek new clinical approaches for psoriasis management.

Man has long struggled against the obstinate diseases using traditional medicine systems. Traditional approaches have now been included within complementary and alternative medicine (CAM) and are often regarded as safe and economical. They also tend to incorporate prevention and rehabilitation in addition to the treatment of psoriasis symptoms. Chinese medicine (CM) is a well-known CAM system. Smith et al. (2009) reviewed a number of clinical studies and found that 43%–69% of psoriasis patients utilise some form of CAM, often in combination with conventional treatments (36). They also showed some evidence for the efficacy of certain CAM therapies.

Some methods of controlling of psoriasis symptoms have been recorded in both the classical and modern clinical CM literature. Although the prevalence of psoriasis in pre-modern China is unknown, diseases that are likely to have been psoriasis have been described in classical texts under a number of different names. For example, a disease that appears to have been psoriasis (named Ganxian) was described in the ‘General Treatise on the Causes and Symptoms of Diseases’ written by Chao Yuanfang in A.D. 610. A disease termed Baichuang was also described in the ‘Comprehensive Summary of External Medicine’ by Qi Kun (1665) (37). However, within the scope of these disease descriptions, classical CM texts may have also included diseases that would not fit the contemporary definition of psoriasis. Therefore, these issues require some careful analysis and clarification. The records of psoriasis treatment in the pre-modern/classical CM literature may provide useful leads for the

development of new psoriasis treatments; however, no systematic compilation or evaluation of these records is available.

The current approaches to finding new leads for drug development include high-throughput screening, data mining of database entries and systematic mining of old herbalist texts, including those from China (38, 39). Experimental studies of the anti-psoriatic effects of Chinese herbs are also in progress (40); however, no studies have integrated the clinical and experimental evidence for individual herbs. This study will provide a comprehensive evaluation of the CM literature and experimental evidence to help identify specific CMs, which may warrant further clinical and experimental investigation.

1.5 Reviews on herbal medicine (HM) for psoriasis

There were several review articles related to the field of HM and psoriasis that has been published when this study began. Most of these were either general reviews of HM or CAM for skin disorders, including psoriasis, or reviews of specific HMs, and some focused on experimental studies. There were 3 reviews on the medical uses of *Aloe vera* and one on shark cartilage (41-44). There was one review is on the use of acitretin in combination with Chinese herbs (45), another on Chinese experimental studies investigating the use of traditional remedies in psoriasis (40), while a third review was on the methodology for evaluating trials of traditional CMs for psoriasis (46).

Four articles had analysed a broader range of HM and/or CAM interventions (36, 47-49). Two of these were general reviews of skin disorders (36, 47). The remaining 2 focused on psoriasis; however, the article by Steele *et al.* (48) was mainly regarding the top 15 plants in common use, and the article by Tse (49) focused on the individual Chinese herbs commonly used in clinical trials.

In reviews of the use of Chinese Herbal Medicine for skin disorders, Koo *et al* (50, 51) provided comparisons between the Western and Chinese Medicine treatments for psoriasis which discussed the use of CHMs topically, orally and in conjunction with ultraviolet (UV) radiation treatment. This approach is similar to that of Western medicine and the reviews

noted that a number of the herbs included in topical HMs that were combined with UV contained photosensitising compounds. Although such similarities are evident, points of difference included the use of multiple HMs in many CHM formulations, the use of syndrome differentiation in the selection of HMs appropriate to an individual case, and the modification of multi-herbal formulae according to the needs of each patient. In a discussion of the Chinese and Western medicine treatments of psoriasis, the expert on psoriasis Ouyang Heng mentioned similar points regarding the Chinese medicine approaches to diagnosis and therapy and also noted that psoriasis can require life-long therapy in Chinese medicine as it does in Western medicine. He made the point that in modern Chinese medicine the diagnosis of psoriasis is based on the same principles as in Western medicine but Chinese medicine adds syndrome differentiation and the approach to treatment varies according to the syndrome and stage of the disease (52).

These reviews were essentially descriptive and did not provide information on selection and exclusion criteria, methodological assessment or meta-analyses. A Cochrane protocol for a comprehensive systematic review of psoriasis treatment with Chinese HMs was published in 2009 (53). However, at the commencement of this study no systematic review on topical or systemic HM for psoriasis was identified.

1.6 Significance of the research

Studies in Europe have revealed that approximately 43% of psoriasis patients utilise some form of CAM, often in combination with conventional treatments (36, 54). In China, HM is extensively used by psoriasis patients. Dermatologists may intentionally use combined conventional and HM treatments to enhance the overall therapeutic effect or reduce the dosage of conventional medications (52, 55). Some methods for controlling psoriasis symptoms have been recorded in both the classical and modern clinical CM literature. Certain CM treatment approaches have attracted the attention of clinical researchers, and a number of clinical trials have been published. However, the quality of these trials appears variable, and there has been no systematic clinical evaluation of CMs for the treatment of psoriasis.

For further development of the clinical management of psoriasis using CM, the clinical efficacy of the various approaches needs to be evaluated in a systematic manner and the results need to be presented in an easily accessible form. Providing an objective scientific evaluation of the best available evidence may lead to the increased adoption of the evidence-based practice by CM practitioners and encourage the adoption of CM methods by other relevant professionals, including dermatologists, researchers and administrators of healthcare services.

A systematic exploration of the results obtained in experimental studies of the individual herbal remedies used in the clinical management of psoriasis should provide useful leads for the development of new psoriasis treatments.

1.7 Aims of the research

The present study evaluates the effectiveness/efficacy and safety of psoriasis treatments using Chinese HMs. The first component of the project is a systematic review of the modern clinical research literature in English and Chinese and quality evaluation of published clinical trials of psoriasis remedies to find the best available clinical trial evidence. This stage of the study will also identify which herbs and formulae, used topically and systemically, are the best candidates for further clinical and/or experimental research. The second component of the present study is an examination of the experimental evidence for the anti-psoriatic effects of herbs identified in the first 2 stages of the study as promising for the topical and/or systemic treatment of psoriasis.

The objectives of this research are as follows:

1) Systematically review the results of modern clinical research published in English and Chinese on the topical use of CM for psoriasis.
2) Systematically review the modern clinical research published in English and Chinese on the oral/systemic use of CM for psoriasis.
3) Identify the best available evidence for the clinical efficacy of CMs topically and orally used in the treatment of psoriasis.

4) Select the herbs and herbal formulae that show the most promising clinical efficacy.
5) Examine the existing experimental evidence *in vivo* and *in vitro* for the anti-psoriatic effects of the individual herbs identified as having the greatest therapeutic potential in the treatment and/or management of the symptoms of psoriasis.
6) Identify the possible mechanisms of action of the most promising herbs.

1.8 Research questions

To realise these research aims within the stated time frame, the following list of research questions was proposed.

The principal research questions are as follows:

1) What is the current state of the clinical evidence for the efficacy and safety of herbal medicine for psoriasis?
2) Which herbs and/or formulas have the best evidence of efficacy in the management of psoriasis?
3) Which herbs show the best evidence of anti-psoriatic activity based on the combination of clinical and experimental studies?
4) What are the likely mechanisms of action of the most promising herbs and/or their constituents?
5) What are the implications of the clinical and research evidence for the clinical management of psoriasis and for on-going research?

Chapter 2: The characteristics of psoriasis and related disorders

2.1 Pathophysiology of psoriasis

2.1.1 Genetics of psoriasis

A study of psoriasis in Australian twins has estimated that its level of heritability is approximately 80% (56). Among psoriasis or psoriatic arthritis (PsA) patients, the family history includes these conditions in 52% and 41% of cases, respectively (57). With 1 parent suffering from the disease, the child has a 16% chance of contracting it; this chance increases to 50% if both parents are affected (2).

Lowes *et al*. (2007) have summarised the genetic background associated with psoriasis (58). As many as 10–20 chromosome regions have been considered to be harbouring candidate psoriasis genes. However, only a small proportion of these have been confirmed. Several potential psoriasis susceptibility loci (*PSORS1* to *PSORS12*) have been mapped to different chromosomal regions. The class I region of the major histocompatibility complex (MHC) locus cluster has been strongly associated with psoriasis; however, its low penetrance of approximately 10% suggests that other factors may also be involved. It is now accepted that the main susceptibility locus *PSORS1* (psoriasis susceptibility 1) is contained within MHC, on chromosome 6p21. Associations between psoriasis and human leukocyte antigen (HLA)-Cw6 have been reported in many different populations. This supports the proposal that a psoriasis susceptibility gene is located in the MHC cluster. Moreover, changes in the HLA-C activity are likely to affect psoriasis susceptibility because HLA-C is involved in the process of immune self-recognition.

The exact function of *PSORS1* is still to be confirmed; it is not even clear whether *PSORS1* is a classical MHC allele or a regulatory variant. The immune system and keratinocyte differentiation may be adjusted by some predisposing polygenes. Immune synapse regulation can be affected by common variants in the *SLC9A3R1*/*NAT9* region, loss of a potential RUNX binding site and variants of the lymphoid phosphatase *PTPN22*. At least 4 other

autoimmune diseases are also affected by R620W polymorphism of *PTPN22*. Associations with genes encoding other immune system components, IL-12, IL-19/20 and IRF2, have also been reported. Chromosome 17q25 has been associated with a family history of psoriasis. Patients suffering from psoriasis present with autosomal-dominant seborrhoea-like dermatitis and psoriasiform expression caused by alterations in zinc finger protein 750 (ZNF750). Because the alteration generally occurs in keratinocytes rather than in fibroblasts (it is even rare in CD4 lymphocytes), keratinocytes should be the main site of the defect (58).

2.1.2 Psoriasis-precipitating factors

a) Trauma:

Koebner phenomenon can be triggered by some physical traumas, chemical injuries and inflammation, abrasions, excoriations, laceration, scarification, rubbing, incision, surgery wounds, and others. This phenomenon is characteristic in psoriasis patients; new psoriasis lesions form at the site of injury in previously unaffected areas. While the disease is active, the phenomenon tends to aggravate. The incidence of Koebner phenomenon among psoriasis patients is approximately 5%–50%. In patients with an early onset, this tendency seems to be stronger; relapses are frequent and have to be controlled with multiple therapies (59).

A reverse Koebner phenomenon can be caused by similar skin injuries; the original psoriatic lesions may clear after skin stimulation. In a 24-patient study, in response to standard skin injuries to psoriasis-affected and unaffected areas, 67% of subjects displayed a reverse Koebner reaction and the proportion of positive Koebner reactions was 25%. The Koebner reaction in psoriasis was found to be of an ‘all-or-none’ type, i.e. if the reaction occurs at 1 injury site, all the injured sites will react in the same manner. Similarly, psoriasis did not develop in the unaffected area after its disappearance from the traumatised area. In terms of the relationship between the disease activity and the Koebner reaction, the former cannot predict the latter but the latter can predict the former (60).

b) Infection:

The incidence of psoriasis linked to bacterial or viral infection ranges from 15% to 76%. Tonsillitis and upper respiratory infections are clearly associated with acute guttate psoriasis. A strong association has been found between streptococcal infections and HLA B13 positivity in patients, which may be caused by insufficient levels of anti-streptolysin-O. Throat infection with beta-haemolytic streptococci can induce and aggravate plaque psoriasis. The human 50-kDa keratin type 1 protein shows a substantial homology with the streptococcal protein M6. A certain degree of cross-reactivity with anti-streptococcal antibodies may be caused by this similarity; this may be linked to the pathogenesis of post-streptococcal psoriasis. During the activation of T cells, keratinocytes may present determinants, which will be identified by T cells as epitopes on beta-haemolytic streptococci. In cases of local skin infections, psoriasis may also be aggravated by superantigens secreted from *Staphylococcus aureus* or *Candida albicans* (59).

A linkage between severe psoriasis and human immunodeficiency virus (HIV) infection has been considered because HIV-1 infection often exacerbates existing psoriasis or triggers the onset of this disease. However, the mechanism underlying this phenomenon seems to be related to comprehensive immunodeficiency of patients rather than their immune reaction to HIV. Psoriasis is considered to be a T-cell-mediated disease. However, CD4+ T cells can still be recruited into the lesional skin in psoriatic patients without acquired immunodeficiency syndrome (AIDS). Besides, T cells may be activated by HIV that acts as a superantigen (59). Some studies and case reports substantiate a close association between the 2 diseases. Psoriasis may be worsened by AIDS (61) but can also regress during terminal AIDS (62).

c) Smoking:

Cigarette smoke contains a complex mixture of substances, including nicotine and carbon monoxide. Gender, genetic background, nicotine dose and concentration may affect the impact of smoking on psoriasis. A case-control study with 560 psoriatic patients analysed the

association between the onset of psoriasis and smoking habits. The overall odds ratio (OR) for psoriasis was higher for current and former smokers [OR, 1.7; 95% confidence interval (CI), 1.1–3.0 and OR, 1.9; 95% CI, 1.3–2.7, respectively] than for non-smokers. Among former smokers, males were at a higher risk of psoriasis (OR, 2.1; 95% CI, 1.3–3.5) than females (OR, 1.2; 95% CI, 0.6–2.2). In contrast, the risk in the current female smokers was higher than that in the current male smokers. There was no significant difference between different types of cigarettes, consumption or smoking styles. A clear association has been established between smoking and pustular psoriasis (OR, 5.3; 95% CI, 2.1–13.0) (63).

d) Drinking:

There is no confirmed direct association between alcohol consumption and psoriasis, despite a potential connection between alcohol abuse or alcoholism and psoriasis. The morbidity of psoriasis may be affected by alcoholism; alcohol misuse increases a risk of liver disease and unfavourable drug interactions (59).

e) Exposure to sunlight:

Sunlight improves the lesions of most psoriasis patients; however, the condition of 10% of patients may worsen (2).

f) Endocrine factors:

The condition of women with psoriasis frequently improves during pregnancy and relapses postpartum. Psoriasis has also been associated with hypocalcaemia and hypoparathyroidism (2).

g) Drug effects:

Some psoriasis patients react against non-steroidal anti-inflammatory drugs (NSAIDs). When the application of systemic steroids, potent topical steroids or efalizumab is discontinued, a ‘rebound’ phenomenon may occur. The severity of psoriasis can also be

increased by some drugs such as antimalarials, beta-blockers, interferon (IFN-α) and lithium (2)

h) Emotional factors:

Stress is likely to lead to deterioration in some psoriatic patients (2).

2.1.3 Main mechanism of psoriasis

The main mechanism of psoriasis is likely to be related to epidermal hyperproliferation, abnormal differentiation of keratinocytes, inflammation and angiogenesis (64). Psoriasis is now considered to be an autoimmune disease rather than just an epidermal condition. T cells play a crucial role in the pathophysiology of this disease (65). After bone marrow transplantation from a donor without the disease, psoriasis in the recipient can clear (66) and it can be transmitted as a result of bone marrow transplantation from a patient with psoriasis (64, 67). Psoriasis patients respond well to DAB389IL-2, a drug directed at T cells bearing interleukin 2 receptors, without any effect on keratinocytes, indicating that T cells play a major role in the induction of psoriasis. Similarly, ciclosporin, which mainly inhibits the activation of T cells, is used as a highly effective systemic treatment for psoriasis (65).

Lebwohl (65) has proposed an immunological and inflammatory mechanism in which T-cell response is centralised (Fig. 2.1). Unidentified antigens can initiate this response by maturation of Langerhans cells, the antigen-presenting cells in the epidermis. The cells then move to regional lymph nodes where naïve T cells are activated by the interaction with the previous antigen-presenting cells. The activation of T cells is based on at least 2 pathway signals. When a T-cell receptor encounters an antigen presented by MHC, the first signal starts the induction. The second signal can control message delivery from antigen-presenting cells to T cells by co-stimulatory signal induction on the surface of the resting T cell. This occurs when lymphocyte functional antigen (LFA)-3 stimulates CDs, B7 stimulates CD28 or intercellular adhesion molecule -1 (ICAM-1) stimulates LFA-1 (Fig. 2.1). After T-cell interaction with the antigen-presenting cells, T cells proliferate and memory T cells are formed. These cells join the blood circulation and finally infiltrate the endothelium of the

inflamed areas. LFA-1 on T cells interacts with ICAM-1 in the endothelium, which is necessary for the adherence of T cells to the affected area. At the same time, T lymphocytes can encounter the initiating antigen and secrete type-1 cytokines (Th1), mainly including interferon-gamma (IFN-γ), interleukin-2 (IL-2) and tumour necrosis factor alpha (TNF-α), which can lead to the proliferation and parakeratosis of keratinocytes and appropriate angiogenesis. Other cells and molecules may also affect the condition. Some chemokines may guide T cells towards the inflamed skin. When they encounter antigen-presenting cells, $CD8^+$ T cells can mature, proliferate, join the blood circulation, return to the affected skin where the initiating antigen remains and secrete IFN-γ (65).

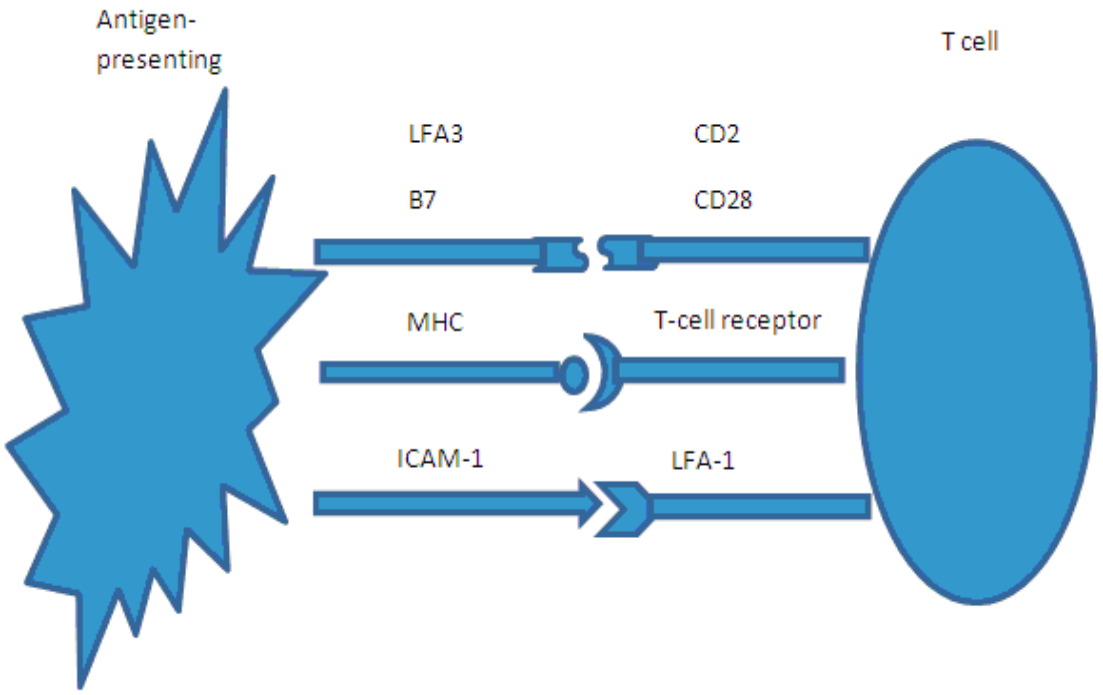


Fig. 2.1 Activation of T cells (adapted from Lebwohl, 2003)

The subsequently accelerated proliferation of keratinocytes decreases the epidermal transit time from approximately 23 days in the normal skin to only 3–5 days in psoriasis patients. This alters the natural process of the proliferation of keratinocytes in which they just slowly travel towards the surface, where they predominate, following their growth at the bottom

(basal) layer. The differentiation of keratinocytes is also disturbed because they cannot lose their nuclei in a normal manner. Therefore, the 2 main epidermal features of psoriasis are formed: scaling (thickened skin) and parakeratosis (abnormal differentiation) (1).

T-cell cytokines activate epidermal keratinocytes, which can promote angiogenesis (vascular proliferation) (68). Keratinocytes, activated T cells and endothelial cells also synthesise vascular endothelial growth factor (VEGF), which is likely to be a key factor in angiogenesis during psoriasis (69). VEGF and its receptors are overexpressed in human psoriatic lesional and non-lesional epidermis. VEGF levels reflect psoriasis activity, severity and joint involvement. The typical manifestations of psoriasis, such as vascular changes (increased dermal vascularity), epidermis alterations and inflammatory infiltrates can be affected by VEGF *in vivo*. VEGF inhibitors can reverse or inhibit some of these processes (68).

2.1.4 Histopathological changes

There are several characteristic changes associated with psoriasis. For example, Lowes *et al*. (2007) stated five features on the histopathological aspect:

a) Substantial thickening of the epidermis: This is caused by the accelerated proliferation of keratinocytes; epidermal rete ridges lengthen to form projections that are long, thin and downward-oriented to adapt to the downward undulations of the epidermis.

b) Differentiation of keratinocytes with regenerative maturation: Keratinocytes switch from the normal growth program to regenerative maturation, normally only required during wound healing.

c) Abnormal terminal differentiation of keratinocytes: Terminal differentiation begins in the granular layer of the epidermis; however, in the absence of this layer in psoriatic lesions, hyperproliferation and abnormal differentiation of keratinocytes results in surface scale formation.

d) Parakeratosis: Keratinocytes still have cell nuclei after shaping the stratum corneum because their differentiation is incomplete. Psoriatic corneocytes (terminally differentiated keratinocytes) cannot stack normally, release lipids or adhere effectively, which leads to scaling and causes further damage to the protective barrier.

e) Presence of neutrophils and marked infiltration of mononuclear leukocytes: They are found in small foci of the stratum corneum and in the epidermis. In particular, the mononuclear leukocytes [T cells and dendritic cells (DCs)] may lengthen, and multiple microvessels form in epidermal rete. These vessels greatly dilate, causing the redness observed in the psoriatic lesions. Large numbers of numerous lymphocytes and monocytes adhere to endothelial cells to be recruited by high endothelial venules (58).

2.2 Diagnosis

2.2.1 Clinical features

In general, psoriasis can be diagnosed on the basis of its clinical features. Illustrations of the symptoms and signs and the types of psoriasis can be found in the books by Buxton and Morris-Jones (1) and Weller *et al* (2). The clinical morphology of psoriasis lesions is so characteristic that the diagnosis is not difficult. Only in special cases such as psoriatic erythroderma, Sèzary syndrome and erythrodermic eczema, a biopsy may be required (11).

Psoriasis is a papulosquamous issue on the body surface. The lesions can be easily distinguished from other papulosquamous diseases such as tinea infections, pityriasis rosea and lichen planus. Psoriasis lesions are well delimited, circular red papules or plaques. On the basis of the diameter of the raised lesions, the papulosquamous lesions can be categorised as scaling papules (<1 cm) and plaques (>1 cm) (3). Plaque psoriasis is the most common type, constituting 90% of all the cases. The plaques activate at the edge of lesions and surround the fast progressing lesions; the normal skin is visible in the lesion centre (70).

Some non-coherent scales with dry, grey or silvery–white appearance cover the lesions, and shiny erythaema is visible under the scales (3, 71). Removal of the scales can lead to

pinpoint bleeding (Auspitz sign) (71). In 20% of psoriasis patients, the lesions may appear in non-lesional areas after local stimulation or trauma (Koebner phenomenon) (3, 71).

The lesions are often symmetrically distributed and tend to occur on the scalp, umbilicus, lumbosacral area, extensor aspects of elbows and knees and body folds (3, 11).

Nail abnormalities may occur in psoriasis patients, particularly in PsA (3, 71). These changes may evolve from small pits to substantial deformities, including onychodystrophy, which can make the entire nail yellow and keratinous (71).

As a papulosquamous skin disorder, psoriasis varies widely with regard to the manifestation of lesions, their form, size, number, location and severity. Small tear-shaped papules can be found in guttate psoriasis patients, and pustules may occur in pustular psoriasis patients. Erythrodermic psoriasis may manifest itself as generalised erythaema and scaling. From a chronic and stable condition, the disease may progress to an acute status, covering wide areas and developing serious symptoms (3).

2.2.2 Diagnosis and assessment tools

The Committee on Guidelines of Care and the Task Force on Psoriasis of the American Academy of Dermatology defined the disease as ‘A chronic skin disease that is classically characterised by thickened, red areas of skin covered with silvery scales’ (72). Psoriasis Diagnosis and Management of Psoriasis and Psoriatic Arthritis in Adults, a national clinical guideline created in Scotland, pointed out that the diagnosis of psoriasis may be easily confirmed on the basis of its clinical appearance. As the commonest presentation of the disease, psoriasis vulgaris (chronic plaque psoriasis) manifests itself as characteristic grey or silvery–white scales and well-delimited shiny red plaques. The lesions are symmetrically distributed; they usually affect the scalp and extensor surfaces of limbs, although any part of the body surface can be involved. However, scaling rarely occurs on the genital area, in body folds or on the palmoplantar skin (4).

In general, the severity of psoriasis can be categorised into 3 levels on the basis of the affected body surface area (BSA) (73):

a) Mild psoriasis: less than 5% of the skin area;
b) Moderate psoriasis: from 5% to 15% of the skin area and
c) Severe psoriasis: more than 15%–20% of the skin area

The abovementioned clinical diagnosis may be not very precise or reproducible in terms of severity measures (74). The known biomarkers that may trace or predict psoriasis activity, such as C-reactive protein, soluble adhesion molecules and soluble cytokine receptors, are often not available or are unreliable (70). The use of easily available, practical assessment tools could assist in precise evaluation of the condition.

There are numerous tools for assessing the clinical severity of the disease and its effect on the daily quality of life (QoL). The tools for severity assessment are mainly used to establish the activity of psoriasis rather than the validity of management, and Psoriasis Area and Severity Index (PASI) is the most frequently used measure. The tools for QoL evaluation are often applied in the form of a QoL questionnaire, and Dermatology Life Quality Index (DLQI) is the most used instrument (4). The correlation between PASI and DLQI is rather poor, and DLQI can alter with the improvement of PASI. Both PASI and DLQI are applied in clinical practice to characterise the 2 aspects of the disease (3).

2.2.3 Types of psoriasis

Psoriasis can be classified into 2 types: common pattern and less common pattern. The former includes plaque psoriasis (psoriasis vulgaris), guttate psoriasis, scalp psoriasis, nail psoriasis, flexure psoriasis and palm and sole psoriasis, while the latter includes napkin psoriasis, acute generalised pustular psoriasis and erythrodermic psoriasis (2).

Plaque psoriasis (psoriasis vulgaris:

Plaque psoriasis, also known as psoriasis vulgaris, is the most frequent type that is diagnosed in 90% of the cases (75). In general, this type of psoriasis expresses circular, oval or nummular (coin-sized) plaques with well-circumscribed lesions. The lesions may develop from some early flat erythaematous macules (less than 1 cm in diameter) and later form coalesced plaques (over 1 cm in diameter). Woronoff's ring (a white blanching ring) may appear to be circling the affected sites (3).

Plaque psoriasis frequently occurs on the trunk, limbs and elbows, particularly on the extensor surfaces such as the lower back and extensor surfaces of the knees. This type of psoriasis can also appear on flanks and the umbilicus. Lesions of this type are likely to show a seborrheic distribution, appearing in areas such as eyebrows, cheeks and nasolabial folds as well as on the scalp and scalp line. Breasts or scapular areas are also often involved. In comparison with the classical form, these types of lesions are thinner (<0.75 mm) and their scales look more 'waxy' (75).

The plaques may gradually evolve into several different forms as follows (3):

a) Psoriasis gyrata: Most plaques form bent linear patterns.
b) Annular psoriasis: Circular lesions arise after central clearing.
c) Psoriasis follicularis: Some tiny plaques with scales appear at the openings of pilosebaceous follicles. (See reference 1 & 2 for illustration(s))

Guttate psoriasis:

The term 'guttate' is derived from the Greek word *gutta* that means 'drop' (3), which reflects the manifestation of guttate psoriasis: numerous tear-shaped small plaques (<1cm) with scales (75). In guttate psoriasis, the trunk is typically affected; this type is prevalent among children. It often follows an acute infection by group B haemolytic streptococci. The number of lesions often increases to 5–10 and sometimes can even reach over 100 (3). The salmon pink lesions persist during a 3-month period. They suddenly appear in the first month, remain during the second month and finally clear in the third (75). Guttate psoriasis usually

appears in children, whereas chronic plaque psoriasis develops in adults. Approximately, one-third of guttate psoriasis patients develop a chronic plaque disease later in life (3). However, some plaque psoriasis patients develop guttate psoriasis after a streptococcal infection (75). (See reference 2 for illustration(s))

Scalp psoriasis:

The scalp is frequently affected, and scalp psoriasis is often the earliest sign of this disease (75). The scaling area is often crisscrossed by the normal skin. Sometimes, palpating the lesions supplies better evidence than visual examination (2). In this type, the lesions are not symmetrical as observed in other types of psoriasis. The lesions rarely overflow the scalp line but tend to locate in the posterior auricular area; they vary from localised to diffuse and from thick to thin. The hair-bearing skin can also be affected (75). (See reference 1 & 2 for illustration(s))

Nail psoriasis:

The nails are affected in approximately 50% of psoriasis patients; they are more frequent in PsA patients. There are several types of nail lesions (70):

a) Pitting: the commonest form that can be seen in oblique light;
b) Onycholysis: the separation between the nail bed and plate;
c) Oil spots: orange–yellow stains located in the sub-ungual area and
d) Dystrophy: phenomenon similar to pitting. (See reference 1 & 2 for illustration(s))

Flexure psoriasis:

In comparison with other types, flexure psoriasis presents as thin lesions with fewer scales and more erythaema. The affected areas are the folds in the body surface, such as the axillae, infra-mammary region, inguinal folds and gluteal cleft. Physical or biological factors, for example, friction or candidiasis, may aggravate the condition (75). (See reference 1 & 2 for illustration(s))

Palm and sole psoriasis:

This type of psoriasis causes yellow, sterile pustules within areas of the erythaema, with scaling on the palms and/or soles. Dark brown colouration and scale/crust may develop when the pustules become tender and fade (3). Among patients with this psoriasis type, 25% also suffer from chronic plaque psoriasis. This type is still categorised as a subtype of psoriasis in many specialist textbooks. However, genetic factors involved in this type of psoriasis are different from those involved in psoriasis vulgaris. Furthermore, these 2 types have different demographics. Plaque psoriasis patients tend to be female (9:1 ratio of female to male patients) and smokers, and the condition develops between 30 and 40 or 40 and 50 years of age. Therefore, palm and sole psoriasis should be considered to be a comorbidity rather than a subtype of psoriasis (70). (See reference 2 for illustration(s))

Napkin psoriasis:

This condition occurs at the napkin (nappy/diaper) area in an infant and provides the first clue of psoriatic susceptibility of the baby. In general, this condition is short-lived. However, it reveals an increased risk of contracting psoriasis later in life (2). (See reference 1 & 2 for illustration(s))

Acute generalised pustular psoriasis:

This type of psoriasis, also known as von Zumbusch psoriasis, is rare; however, it is an active and unstable form of the disease. The patients usually have to be hospitalised. The condition may be triggered by the withdrawal of systemic or potent topical corticosteroids or by infections. The patients have fever and red, painful flare sites with monomorphic and sterile pustules that may fuse to form sheets (3). (See reference 1 & 2 for illustration(s))

Erythrodermic psoriasis:

This type of psoriasis is also rare and often occurs suddenly; it can be triggered by several factors such as irritation by tar or dithranol, drug eruption or withdrawal of potent

external/internal steroids. It often affects most of the body surface, resulting in a fiery red, peeling skin. Patients often shiver, and their skin feels hot and uncomfortable (2). It is likely that the thermoregulatory function of the skin is affected. The pathological changes can be life-threatening because pneumonia or congestive heart failure may develop (3). (See reference 1 & 2 for illustration(s))

2.2.4 Differential diagnosis:

In general, cases of classic psoriasis are unlikely to be confused with other diseases. However, sometimes, psoriatic symptoms are atypical, and the diagnosis becomes uncertain. It may be necessary to apply additional measures to ensure correct diagnosis. A detailed skin examination, skin biopsy and other tests may be required for asymptomatic patients and for examining disease evolution (76). Differential diagnosis of psoriasis involves the assessment of several inflammatory, infectious or neoplastic conditions (75):

Atopic dermatitis: It appears on the flexural surfaces of the body with 'weeping' lesions and a type of erythaema but without scales. Patients complain of severe itching and have slight nail abnormalities. Their personal and/or family history may support the diagnosis.

Dyshidrotic eczema: Vesicles may arise at the sides of fingers, toes and webs, with tapioca-like fluid. Patients complain of severe itching.

Nummular eczema: It frequently occurs at distal leg areas. The lesions are small, coin-shaped (nummular) or oval. The scaling is less silvery than that in psoriasis.

Pityriasis rubra pilaris: Its scaly plaques resemble psoriasis. Pityriasis rubra pilaris shows acral distribution of 'islands of sparing', which are patches of the unaffected skin. Changes in the nails appear in narrow bands. This condition also causes characteristic changes in follicular orientation and lesion colour.

Pityriasis rosea: It usually begins with a single 'herald patch' lesion on the trunk, which is a salmon red plaque approximately 2–10 cm size, followed by smaller patches 1 or 2 weeks

later. This disease can last for 2–3 months. With its 'Christmas tree' distribution and collarette scale, it is easily distinguished from guttate psoriasis.

Tinea capitis: This is an adenopathy caused by a fungal infection; hair shafts are broken and alopecia occurs.

Tinea corporis/tinea cruris: The lesions are not symmetrical. There is unaffected skin in the centre of the lesion; however, the border displays active scaling.

Tinea paedis: Some forms affect the toe-web spaces, causing chronic scaling, fissuring and maceration; other types of this infection may attack the soles and sides of the foot. A papulosquamous ('moccasin-like') pattern of scaling may develop.

Tinea unguium: This disease affects toenails without causing pitting. The distribution is not symmetrical.

Candidiasis and genital candidiasis ('balanitis'): *Candida* forms peripheral pustules, known as 'satellite' pustules. Crural areas and finger webs may be affected and appear moist and whitish. In genital candidiasis, pustules with erosion and fissures arise on the genitalia. Spread erythaema can also be observed.

Secondary syphilis: The patients have a history of chancre. During 2–6 months after the initial infection, the disorder will develop. First, it presents as erythaematous exanthaema, followed by a guttate-like papular eruption. Following this, copper-coloured papules develop around the trunk and limbs. Finally, the palms and soles are affected. Mucosal lesions and condyloma lata commonly appear on the mouth and genitalia. This condition can be identified with a treponemal antibody test.

Squamous cell carcinoma *in situ* (Bowen's disease): As observed in psoriasis, separate erythaematous plaques are well-circumscribed and covered with scale. The lesions arise on the sun-exposed areas such as the ears, scalp, lower lip, upper chest, back and hands. The disease can be suspected when a prolonged treatment fails and/or evolves into an invasive

disease. Fewer scales and a dull appearance of erythaema can distinguish this condition from psoriasis. It can occur on any part of the body, although the lower legs are most commonly affected.

Cutaneous T-cell lymphoma (CTCL): This group of disorders includes mycosis fungoides, lymphoma cutis and Sézary syndrome. Erythaematous patches may develop into plaques and further into nodules or tumours. Sometimes, erythaematous shapes may be formed. In the 'patch' stage, it is easily confused with psoriasis and is often not identified correctly in biopsy specimens. With disease progression, identification may be easier using a series of biopsies and some specific techniques such as T-cell receptor gene rearrangement and flow cytometry. When topical drug administration has no effect on the isolated psoriasiform plaques, this disorder should be suspected. The specific tests should be performed, including a complete blood count with a peripheral smear.

2.2.5 Comorbidities associated with psoriasis

PsA: This may be an early example of associated diseases in dermatology. In 1818, Alibert observed the symptoms and called the disease 'psoriasis arthritic' (11). PsA often presents as symmetric polyarthritis or asymmetric oligoarthritis (<5 joints), with symmetric polyarthritis being the most common. This disease has variants such as distal arthritis, spondyloarthritis (sacroilitis and spondylitis) and arthritis mutilans. PsA also includes enthesitis, dactylitis and tenosynovitis. Patients whose back pain lasts for more than 3 months should be screened using the Assessment of SpondyloArthritis International Society (ASAS) criteria. The criteria are age of onset less than 40 years, insidious onset, pain relief by exercise but not by resting and occurrence of pain at night. The diagnosis can be reached when at least 4 of these 5 criteria are fulfilled (4).

Systemic disorders: The associated conditions may be cardiovascular disease, type 2 diabetes mellitus (DM), metabolic syndrome, Crohn's disease and cancer. Psychological issues such as depression may also follow the clinical appearances of psoriasis (70). In particular, severe psoriasis or PsA is associated with a high risk of cardiovascular disease and diabetes. The

patients should be assessed on the basis of body mass index (BMI), DM screening, blood pressure measurement and lipid profile (4).

2.3 Therapy

In general, the management of psoriasis includes 4 types of treatment: external/topical treatments, phototherapy, systemic medication and biological therapies. While deciding on the appropriate management, many physical and psychosocial factors should be taken into account. Some of the most important factors are the number of lesions, affected BSA, phenotypical characteristics and QoL of the patient (75). Therefore, psoriatic treatment should be individualised. This may be subject to the condition, location, impact, comorbidity and risk factors of the disease as well as patient compliance with the treatment (6).

2.3.1 Topical treatment

Topical treatment is still the most frequently used method of treating most psoriasis patients, particularly when the condition is limited. Individual lesions can be treated separately. However, this type of management is time-consuming and may cause lack of patient compliance. It should be individualised and simplified as far as possible. The applications of different preparations such as creams, lotions, foams, sprays, ointments and gels should also be considered (6).

Numerous textbooks and many reviews have been written on the topic. Recommended treatments include topical glucocorticoids (GCs), vitamin A derivatives (tazarotene), vitamin D derivatives (calcipotriol, calcitriol, paricalcitol and tacalcitol), tar preparations and anthralin. The literature in this field also contains many relevant indications and contraindications, application instructions and descriptions of side effects (77).

Topical corticosteroids

The types of corticosteroids used depend on the location of the affected region. Ointments are suitable for thicker skin, such as the skin on the elbows and knees, whereas creams are suitable for thinner skin. For the scalp, foams, gels and shampoos are available. In general,

corticosteroids can be divided into 4 groups according to their clinical efficacy and vasoconstriction subsequence (75):

Class 1(very potent): ≤600 times more potent than hydrocortisone;

Class 2 (potent): 100–150 times more potent than hydrocortisone;

Class 3 (moderate): 2–25 times more potent than hydrocortisone and

Class 4 (mild): 0.5%–2.5% of the potency of hydrocortisone.

Because the efficacy of corticosteroids appears to be inversely proportional to their toxicity, it is often recommended that they should be applied less than 3 times per day, for up to 2 consecutive weeks (no more than 50 g a week). Corticosteroids should not be used on the face or in flexures. New innovative products have been developed, which can be applied only during weekends to minimise complications. The treatment can also be combined with non-steroidal medications. After the lesions respond to the initial intervention, the medication can be changed to one of the less potent types (6).

GCs, which are used in the treatment of psoriasis, include prednisone/prednisolone, methyl-prednisolone and fluorinated GCs (i.e. dexamethasone and betamethasone). As main immunosuppressive and anti-inflammatory drugs, GCs are applied widely and show high efficacy. The effect may be associated with genomic (sequential interaction with cytosolic GC receptors and the genome) or non-genomic aspects (interaction with cellular membranes). The former manner of action is more likely to affect the efficacy. It often involves transrepression and transactivation, which inhibit and activate the synthesis of regulatory proteins, respectively. Furthermore, transrepression appears more relevant to the anti-inflammatory effects because it inhibits the synthesis of proinflammatory cytokines or cyclooxygenase. The selective GC receptor agonists (SEGRAs) regulate their efficacies via the desired transrepression effect rather the than transactivation activity exerted by conventional GCs (78).

Vitamin D_3 derivatives

Three Vitamin D_3 derivatives are available as the current first-line intervention for plaque psoriasis: calcitriol, tacalcitol and calcipotriol. These vitamin D_3 derivatives can be used as monotherapy but are often combined with topical steroids in ointment, cream or solution. The common application frequency is once or twice a day. There are several commonly available products, which are safe in if used within a maximum recommended dose (6):

Table 2.1 Common Vitamin D_3 analogues for psoriasis

Specification	**Form**	**Weekly maximum recommended dose**
Calcitriol 3 μg/g	Ointment	210 g
Tacalcitol 4 μg/g	Ointment	70 g
Calcipotriol 50 μg/g‡	Cream, ointment, Scalp solution	100 g of cream or ointment, 60 mL of scalp solution
Calcipotriol 50 μg/g + betamethasone dipropionate 0.5 mg/g	Ointment	100 g

‡Generic name calcipotriene in USA.

Ortonne *et al*. have found that calcitriol ointment is superior to calcipotriol ointment in its efficacy and is better tolerated on sensitive areas such as the face, hairline, retroauricular areas and flexural skin (79). With its once-daily application, tacalcitol is regarded as better than calcipotriol (6). However, the efficacy of calcipotriol is slightly higher than that of calcitriol or tacalcitol and is comparable with the efficacy of potent topical corticosteroids (80).

In combination therapy, the use of Vitamin D_3 analogues can reduce the required dose and duration of treatment with other topical drugs, which improves the risk:benefit ratio of management. In particular, vitamin D_3 analogues in combination with topical corticosteroids have shown high efficacy in numerous interventions. This strategy has enabled physicians to reduce the frequency of primary topical interventions in plaque psoriasis (e.g. once-daily applications) and/or minimised the impact of side effects (6).

Vitamin D (calcitriol) can be used to synthesise calcipotriol, tacalcitol and paricalcitol. Their biologically active forms act as agonists of the vitamin D receptor (VDR), which can change the conformation of VDR and affect gene transcription. This may improve cell differentiation, proliferation, immunomodulation and mineral homeostasis (77).

Calcineurin inhibitors

Tacrolimus and pimecrolimus are the 2 agents available for treating psoriasis. These drugs, with immune-modulating and anti-inflammatory properties, do not cause skin atrophy. They can be safely applied to all sensitive skin surfaces, including the head, face, neck, around the eyes and intertriginous areas (6).

Tazarotene

Tazarotene, a retinoid derived from vitamin A, is used once a day in the management of psoriasis vulgaris. It can be applied as a gel or cream. Tazarotene is not very efficacious on its own and is often used in combination with other drugs. In comparison with calcipotriol, tazarotene appears less effective and causes more local irritation. It should not be used by pregnant women as it carries a risk of teratogenicity. For lactating women, its use is restricted to localised lesions (6).

The recommended indication of tazarotene is chronic stable plaque psoriasis that involves no more than 20% of the skin surface and appears on the trunk and limbs. It is sparingly used only once a day, usually at night, for a period of up to 12 weeks. Preparations of 0.05% and 0.2% tazarotene are available. If irritation arises, only the weaker form should be used; if the problem still persists, it should be applied every 2 days in combination with a topical steroid. Tazarotene can control emissions, induration, scaling and redness of the lesions. Its efficacy is associated with its selective affinity for retinoic acid receptors (RAR) that affect keratinocyte proliferation, differentiation and infiltration of dermal inflammatory cells (2).

Coal tar and dithranol (anthralin)

Coal tar and dithranol (anthralin) have been used in the management of psoriasis for a long time. In 1921, Goeckerman introduced the combined treatment using tar and phototherapy. In 1948, Ingram introduced another treatment using dithranol and phototherapy. Both the drugs are available in a series of different vehicles as ointments, pastes, shampoos and solutions. Because dithranol often stains clothes and irritates the skin, it is only applied for a short time (≤1 h) and then removed. This is called a 'short-contact' treatment. Although tar preparations in shampoo have been used for scalp problems, few studies have reported long-term remissions. Therefore, these treatments do not seem very competitive, particularly after the launch of vitamin D3 derivatives. Vitamin D3 derivatives show a greater efficacy and lower irritation incidence than coal tar and dithranol treatment (2).

2.3.2 Phototherapy and photochemotherapy

Phototherapy and photochemotherapy use ultraviolet light at 200–400 nm. The treatment can be categorised into 3 types:

Ultraviolet light C (200–290 nm): it has germicidal properties,

Ultraviolet light B (290–320 nm): this wavelength range is used most often in the management of psoriasis, particularly its 311–313 nm (narrowband UVB) variant, which is most effective, and

Ultraviolet light A (320–400 nm): also called UVA, used for psoriasis in combination with photosensitisers such as methoxsalen (8-methoxypsoralen) (75).

Radiophysical effects and therapeutic mechanisms

The efficacy of UV irradiation in clearing psoriasis depends on the wavelength of the light used during this treatment. The most effective wavelength seems to be 304–313 nm, the UVB range. Shorter wavelengths (less than 300 nm) are associated with more side effects such as erythaema and burns. Therefore, the minimal erythaema dose (MED), defined as the threshold dose that may produce burns, should be referred to when calculating the daily dose

of UV. In principle, daily MED becomes the customary dosage in the treatment of psoriasis. The most effective lamps are UVB lamps with a strict UVC filter and UVA lamps. Phillips UV-B TL01 lamp (Philips, Germany) is the preferred instrument for treating psoriasis (81).

UV irradiation can supress lymphoproliferation and the activity of peripheral natural killer cells. It also has a direct effect on cytokine production in both Th1 and Th2 T-cell populations. UV irradiation can affect transcription factor binding to DNA. Cis-urocanic acid, formed after UV-B exposure, has been implicated in regulating the activity of epidermal antigen-presenting cells. The suppression of cell-mediated immune function has been shown to be advantageous in treating psoriasis (82). UV radiation has both immediate and delayed effects. The immediate effects include the damage of cell membranes and DNA, induction of cytoplasmic transcription factors and isomerisation of chromophores, which result in substantial cytopathic changes, growth arrest and/or apoptosis. The delayed effects cause alterations in the psoriasis microarchitecture, involving immune response based on Th-1 (81).

Phototherapy (broadband and narrowband UVB)

Although broadband UVB sources were the first to be introduced in the management of psoriasis, they are not much used in current practice. They are less effective than narrowband UVB or psoralen and UVA (PUVA). Broadband UVB treatment exposes patients to substantial doses of low wavelength spectra (<300 nm). This results in a higher risk of non-melanoma skin cancer than that caused by the combination therapy with UVB of 311 nm. The dose starts at 0.7 of the patient's individual MED and increases by 20% of MED per session. The frequency of weekly sessions is set between 3 and 5. Narrowband UVB has better efficacy than broadband UVB and causes fewer side effects. Consequently, the use of broadband UVB has been recently discouraged, and narrowband treatment is now preferred. (81).

The traditional broadband UVA treatment has been almost replaced by narrowband UVB intervention. Narrowband UVB irradiation was first successfully applied in Europe using

Phillips TL01 lamp. UVB-311 nm phototherapy has long been regarded as an appropriate approach because of its high tolerance and acceptable safety. However, there is no single optimal irradiation solution. Regimens can vary depending on the starting dose, irradiation frequency and dose increments. The starting dose should be individually calculated taking into account the allowed MED. Doses of 0.5–1 of MED are recommended, and 0.7 of MED appears to be the most frequently used. Normally, it is necessary to conduct 3 sessions per week. It is not clear whether more than 3 sessions per week would provide better results. With regard to the increment scheme, it is important to limit the damage to only a mild perceptible erythaema with minimal burns. Various increment schemes have been proposed, e.g. 10%–20% per day or 30%–40% per week. As an alternative, 0.01 to 0.05 $J \cdot cm^{-2} \cdot d^{-1}$ increment has been set. It would be useful to achieve a global consensus on this issue (81).

At present, UVB plus tazarotene, vitamin D3 derivatives or systemic agents are the most frequently used combined phototherapies. Interestingly, a 25-year follow-up study using UV radiation plus topical crude coal tar conducted at the Mayo Clinic (Rochester, Minnesota, US) showed the incidence of skin cancer to be similar to the expected incidence (83).

PUVA photochemotherapy

PUVA photochemotherapy is a therapy combining UVA radiation with psoralen. First, patients take a photosensitive drug, 8-methoxypsoralen or 5-methoxypsoralen, in the oral or topical form. Then, they are exposed to UVA light in the wavelength range from 320 nm to 400 nm (6, 69).

Oral PUVA therapy should be continued until the lesions become imperceptible and scaling and intrinsic erythaema disappear. No further maintenance therapy is required. Psoralen can cause the accumulation of insoluble proteins on the lens, which increases the risks of cataracts and retinal damage. Eye protection is necessary during this therapy and for at least 12 h after irradiation (81). Because it carries a cumulative risk of cutaneous malignancy, PUVA has been limited to 150 applications in a lifetime. The increased risk of skin cancer can persist for at least 15 years after the treatment and becomes greater after using

ciclosporin (69). A topical application variant of PUVA photochemotherapy, bath PUVA therapy, has many benefits in comparison with the oral administration method. It has a lower gastrointestinal and hepatic impact and does not require eye protection. Moreover, oral PUVA therapy is not more effective than bath PUVA therapy (81).

In summary, PUVA therapy can be used for most psoriasis types and achieves a complete or partial remission in 70%–90% of cases. The efficacy of PUVA therapy can be increased by the application of topical remedies. Combined PUVA therapy, e.g. with added retinoid treatment, provides even better results than either of the 2 abovementioned interventions. However, PUVA therapy is not suitable for patients with some specific conditions (69):

1) Patients with photosensitivity, skin cancer or aphakia;
2) patients undergoing immunosuppressive intervention;
3) women during pregnancy or breastfeeding; and
4) children.

2.3.3 Systemic and biological treatments

In 1971, methotrexate (MTX) was approved to be launched in the US. Since then, traditional systemic therapy has been used for psoriasis and has become the primary treatment for moderate-to-severe conditions. It is also used for patients not responding to topical treatments or phototherapy. It is also suitable for patients with low QoL or physical restrictions. To decide on a treatment, it is necessary to evaluate each patient carefully. The availability of drugs and individual issues such as the HIV status and disease history (e.g. hepatitis, systemic cancers) should be examined. If traditional treatments are not available or badly tolerated, biological therapy can be offered as an alternative scheme (6). Biological therapies can be categorised into into T-cell-targeted treatments (alefacept, efalizumab) and TNF-α antagonist treatments (infliximab, etanercept and adalimumab). Traditional systemic agents include MTX, ciclosporin, acitretin and fumaric acid esters (69).

MTX

MTX is available for psoriasis patients in the US and Europe. Its main mechanism of action is immunosuppression by specific modulation of cytokine production by T cells. The dose should be as low as possible and individually adjusted to minimise the toxicity during therapy (84).

In general, the starting dose is 2.5–25 mg in a single weekly oral, intramuscular or intravenous administration for a normal-weight adult patient. The dose can be gradually increased until the symptoms are controlled. The total dose should not exceed 30 mg per week (84). To ensure high efficacy, bioavailability and low hepatic toxicity, the oral method is not recommended for the first 6 months. Instead, intramuscular or subcutaneous administration should be used. Tablets may be used later if the treatment is effective and the patient adapts to the regimen well. One weekly dose of tablets can cause problems such as low absorption and digestive disturbances; the tablets are usually administered in 2 or 3 separate doses. For example, the tablets could be administered at 8 pm on Friday, 8 am on Saturday and 8 pm on Saturday. Folic acid (5 mg q.n.) can also effectively improve MTX tolerance (85). Because hepatic toxicity is a primary issue in MTX treatment, liver biopsy should be considered before treatment. Patients on a long-term course of MTX should also be considered for biopsy if their liver function becomes abnormal or the total cumulative dose reaches 1.5 g. MTX can interact with some other drugs such as systemic steroids, trimethoprim/sulphonamides and non-steroidal anti-inflammatories. These drugs should not be prescribed with MTX (86).

MTX provides an affordable, gold-standard regimen for recalcitrant conditions. It is still widely used even after the introduction of new regimens (6).

Ciclosporin (cyclosporin)

In 1979, ciclosporin (cyclosporin) was first applied for treating psoriasis. Today, it has become the first choice among systemic treatments; however, it is often used only for short periods (≤3 months or 4 months). The main limitation of ciclosporin is its renal toxicity; it

can also cause hypertension (85). Therefore, full renal function tests should be considered before the treatment. A series of tests should be conducted: blood pressure, serum creatinine, urea and 2-h creatinine clearance. The first 3 items need to be tested monthly and the last item needs be measured every 3–6 months. When creatinine is above 25% of the baseline data and/or the diastolic blood pressure is higher than 95 mm Hg, ciclosporin administration should be reduced or discontinued (86). The normal starting oral dose is 2.5 mg/kg per day, which can be administered as 1.25 mg/kg b.i.d. The dose is gradually increased by 0.5–1.0 mg/kg per day every 2–4 weeks. A dose of 5 mg/kg per day is regarded as the maximum. The duration of a short course is usually 12 weeks. For young patients, the duration of treatment should not exceed 4 months and the dose should gradually be reduced during the last 2 months (87, 88).

Retinoids

Retinoids are derivatives of vitamin A; etretinate and acitretin are the 2 main substances of this type developed for medical purposes (87). At present, only acitretin is licensed for use in the US and Europe. Its mechanism of action has not been not confirmed till date; it may be associated with immunosuppression, anti-inflammatory effects and modulation of proliferation and differentiation in the epidermis (84).

The initial dose is often 10 mg/day, administered with meals. The daily dose can be increased every 2 or 4 weeks, till the tolerated dose peaks. When the expected tolerance under the maximum dose lasts for 3 months, efficacy can be evaluated. The adjustable dose resulting in a lack of efficacy or intolerance is often as low as 5 mg (87). The main disadvantage of retinoids is their teratogeny and long-term accumulation in the body. Women should not become pregnant before 2 years after discontinuation of the drug (86).

Fumaric acid esters

This treatment has been frequently applied in Germany since 1995. It is a combination therapy using dimethylfumarate and monoethylfumarate. The mechanism of action may be associated with the suppression of hyperproliferation of epidermal cells and T-cell activity.

The initial daily dose is usually 1 or 2 tablets containing 30 mg of dimethylfumarate and 75 mg of monoethylfumarate. The dose can be raised to a maximum of 6 tablets containing 120 mg of dimethylfumarate and 95 mg of monoethylfumarate, divided into 2 daily doses. The use of these drugs in monotherapy of a 3-month duration or combination therapy with topical drugs can result in significant improvements (75).

Infliximab

Infliximab is a monoclonal antibody against TNF-α. This biological agent can achieve significant improvements in the condition of patients (89). Infliximab is often administered by an intravenous drip, usually of least 2-h duration. The dose varies depending on the condition treated. No optimised solution, frequency or dose of infusions has been established till date. However, a recommended starting dose is 5 mg/kg on weeks 0, 2 and 6; this is repeated after 8–12-week intervals (90). Once the efficacy of infliximab reduces, the frequency of infusions should be increased (89).

Etanercept

Etanercept is a recombinant TNF-α receptor fusion protein. It targets human IgG1 via its 2 extracellular ligand-binding domains. The drug has been approved for treating rheumatoid arthritis; its applications in PsA have been fairly successful. Among PsA patients, 87% of cases respond well to etanercept. Approximately 50%–70% of patients improve their PASI after etanercept treatment; it has been reported that 56% of patients using etanercept show a 75% reduction in the PASI score after a 24-week course (65). It is subcutaneously infused, and the recommended starting dose is 50 mg per week for 12 weeks, followed by the same maintenance dosing. This regime offers the optimal balance between cost and effectiveness for 1-year therapy. Combining it with NB-UVB, acitretin or MTX may strengthen its therapeutic action. If etanercept has no or little effect, it can be replaced with infliximab, adalimumab or efalizumab (89).

Adalimumab

Adalimumab is a monoclonal antibody against TNF-α. It can be subcutaneously administered by patients themselves. The dose is 40 mg per fortnight. It has been reported that 54% of patients using adalimumab for 24 weeks can effectively alleviate their condition on joints and skin, achieving PASI 75. This efficacy ranges between that of infliximab and etanercept. After 60-week therapy, 58% of patients achieve PASI 75. The treatment can be combined with other anti-TNF-α drugs. This treatment can prevent radiographic signs of joint destruction or arrest the development of disability. Adalimumab is a good option for psoriasis patients, resulting in considerable improvements in their QoL (6).

Alefacept

Alefacept is a fusion protein targeting IgG_1. With its Fc receptors, alefacept can trigger the apoptosis of CD45RO+ T cells by affecting macrophages and natural killer (NK) cells. CD2 expression in CD45RO+ memory T cells is associated with the psoriasis status. Alefacept suppresses T-cell activation via CD2. Interestingly, neither primary nor acquired immune responses in the patients using alefacept are likely to be affected. A weekly dose, administered by intravenous boluses for 12 weeks, should be 0.025–0.150 mg/kg. A dose of 0.075–0.15 mg/kg can cause 53% reduction in PASI scores. The drug can also be administered by intramuscular injection at a dose of 15 mg/week for 12 weeks. After subsequent 12-week observation, a second 12-week therapy can be implemented. Psoriasis responds well to alefacept administered using either of the 2 methods (65).

Efalizumab

Efalizumab is used for moderate-to-severe conditions. It is a recombinant humanised monoclonal IgG_1 antibody that can block T-cell-dependent functions; it suppresses the responses mediated by T cells. Efalizumab can effectively control T-cell diapaedesis towards the lesional skin. PASI 75 can be achieved by 29.5% of patients using efalizumab for 12 weeks. Furthermore, a 75% reduction in the PASI score can be reached after a 27-month course of weekly injections. Efalizumab is effective in the treatment of plaque psoriasis and the palmoplantar form of psoriasis (75).

Chapter 3: Traditional Chinese Medicine for psoriasis

3.1 Introduction

Psoriasis has been treated in China since ancient times and the accumulated clinical experiences of generations of practitioners have been recorded and systematized into the approaches to the clinical management of psoriasis now used in traditional Chinese medicine. Chinese Herbal Medicine (CHM) is one of the most frequent types of intervention and has played a critical role in the management of psoriasis since ancient times. This chapter examines the history of Chinese medicine and the treatment of psoriasis, the theories regarding the disease, and the schools of thought in its treatment. This is followed by a discussion of the etiology, pathology, diagnosis, and treatment of psoriasis in contemporary traditional Chinese medicine.

3.2 Background of Chinese Herbal Medicine (CHM)

Chinese Medicine (CM) can be traced back as early as around 5,000 years ago. Archaeological findings during the 1970s suggest that medical stone needles were made as early as Neolithic period (91). Chinese Herbal Medicine (CHM), one form of the most frequent and important CM treatments, can be traced to the Xiayu Period (c. 2100-1600 BC 夏禹时代) when medicinal liquors and fermented preparations were applied. In the Shangtang Period (c. 1600-1100 BC 商汤时期), Yi Yin is reputed to have invented decoctions and wrote the *Tang Ye Jing* (汤液经), the first monograph on formulae and preparation (92).

The first medical classic in China, *The Yellow Emperor's Classic of Internal Medicine* (*Huang Di Nei Jing*, 黄帝内经) which probably originated in the Warring States Period (c. 770-221 BC) discussed the use of acupuncture and the principles for the organisation of herbal formula (92). The *Formulae for 52 diseases* (*Wu Shi Er Bing Fang*, 五十二病方) which was discovered in the Ma Wang Dui Tomb which was sealed in 168 BC during the Western Han dynasty (206-24 BC) is the oldest existing medical book that provides herbal

treatments for a wide variety of diseases (93). *Shennong's Classic of Materia Medica* (*Shen Nong Ben Cao Jing*, 神农本草经) completed in Eastern Han Period (东汉) (25 - 220 AD) is the earliest surviving compendium of *materia medica*. Based on the individual herb's effect and toxicity, it divided Chinese medicinal herbs into three grades: high, medium and low. It not only founded the basis of the classification of herbal medicines but also developed the medical thought of *The Yellow Emperor's Classic of Internal Medicine* (*Huang Di Nei Jing*, 黄帝内经). Furthermore, both these classics in combination with *The Classic of Medical Problems* (*Nan Jing*, 难经) established TCM's theoretical system and provided a standard for clinical practice (93, 94).

Zhang Zhongjing, a renowned TCM expert in Eastern Han Period (东汉), established a methods for the composition and application of multi-ingredient herbal formulae in his Treatise on Cold Damage and Miscellaneous Diseases (*Shang Han Za Bing Lun*, 伤寒杂病论) (93). Numerous topical preparations and their applications where described by Ge Hong (281-341 AD) in his *Handbook of Prescriptions for Emergencies* (*Zhou Hou Bei Ji Fang*, 肘后备急方). Lei Xiao (420-477 AD) wrote the first work on the methods for the preparation and processing of medicinal materials: *Lei's Treatise on Processing of Drugs* (*Lei Gong Pao Zhi Lun*, 雷公炮炙论) (95).

In 659 AD, the *Newly Revised Materia Medica* (*Xin Xiu Ben Cao*, 新修本草) which was edited by officials of Tang Dynasty Government was issued. It included 850 herbs in 54 volumes, and has been regarded as the first official pharmacopoeia in the world. In the same era, Sun Simiao wrote two large compendia on medical theory and practice: *Essential Prescriptions Worth a Thousand Gold for Emergencies* (*Bei Ji Qian Jing Yao Fang*, 备急千金要方) and *Supplement to the Essential Prescriptions Worth a Thousand Gold* (*Qian Jing Yi Fang*, 千金翼方), which included about 5,300 and 2,000 formulae respectively. During the Song dynasty (960-1279), there were major developments in CHM (92, 93). In 1076 AD, the Song government established the first manufacturer of standardised medicines whose roles including manufacture, preparation, audit and inspection of medicinal materials. Its compendium of standard prepared formulae, *Prescriptions from the Great Peace Imperial*

Grace Pharmacy (*Tai Ping Hui Min He Ji Ju Fang,* 太平惠民和剂局方), was the first Chinese pharmaceutical preparation standard (96).

Compendia of Chinese medicinal formulae expanded greatly during the Ming (1368-1644) and Qing (1644-1911) Dynasties. *Prescriptions for Universal Relief* (*Pu Ji Fang*, 普济方) was the largest of the TCM formula treatises with 61,739 formulae including topical preparations such as ointments, pills and medicinal liquors. The most well-known book of this period is the *Compendium of Materia Medica* (*Ben Cao Gang Mu*, 本草纲目) which was written by Li Shizhen in the Ming Dynasty. It systematically reviewed the study of Materia Medica up until the 16th century and included 1,892 herbs, about 1,300 formulae and over 1,100 illustrations. It is widely recognized as a masterpiece of pharmacology with its great contributions to the study of formulae and pharmaceutical preparation. In the Qing dynasty, Zhao Xuemin's *Supplement to the Compendium of Materia Medica* (*Ben Cao Gang Mu Shi Yi*, 本草纲目拾遗) supplemented the previous work with an additional 716 new herbs (92, 93).

After Western Medicine (WM) was introduced into China in the early 19th century, many traditional medical practices were gradually replaced by WM as contemporary hospitals that offered surgery and other WM services increasingly became part of the Chinese healthcare mainstream. During this time there were efforts to combine TCM and WM. For example, Zhang Xichun (1860-1933) wrote *Integrating Chinese and Western Medicine* (*Yi Xue Zhong Zhong Can Xi Lu*, 医学衷中参西录) which was published in 1918 is thought to be the first treatise on this topic. Efforts to modernise TCM including CHM have progressed significantly in the last 60 years. Since the 1963 version of the *Chinese Pharmacopoeia* (中国药典), the uses of Chinese traditional medicines and their methods of preparation have been regularly collected and supplemented. These developments have been further shaped into statutory forms as regulatory acts and codes, for example the *Drug Administration Act of the People's Republic of China* (中华人民共和国药品管理法), *New Drug Examination Code* (新药审批办法), and *Good Agricultural Practice of Medical Plants and Animals* (中药材生产质量管理规范). Through these processes CHM has been developed as a

standardised, legally regulated medical system (92, 97).

Since late 19th century, TCM including CHM has spread widely in the world. Especially since the 1970s, it has been gradually acknowledged by more clinicians and researchers as the body of research evidence grows and drug discoveries such as in the field of malaria receive international attention.

3.3 The TCM terms for psoriasis

In contemporary TCM psoriasis is known as Yin xie bing (银屑病), Niu pi xuan (牛皮癣) or Bai Bi (白疕). However, in the traditional literature this disease has been known under a variety of other terms, each of which may also have included other diseases, including: Gan xuan (干癣 'dry scale'), She shi (蛇虱 'snake lesion'), Bai ke chuang (白壳疮 'white shell sore'), Song pi xuan (松皮癣 'pine bark scale'), Ying qian feng (银钱疯 'silver coin lesion'). The features and descriptions of these disorders are summarised below.

3.3.1 Gan xuan (干癣)

The disorder was first documented by Chao Yuanfang in his *Treatise on the Pathogenesis and Manifestations of All Diseases* (*Zhu Bin Yuan Hou Lun*, 诸病源候论) written in the Sui Dynasty (581-618 AD). It presented as white scales which after scratching the skin became dry and itchy. This disease resulted from Wind, Cold and Damp which led to disharmony of qi and blood. Complete Record of Sacred Benevolence (*Sheng Ji Zong Lu*, 圣济总录) of the Song dynasty included a similar description (98). In *Prescriptions for Universal Relief* (*Pu Ji Fang* 普济方) of the Ming dynasty, the pathogens in Gan xuan were mainly thought to be Wind together with Damp and Heat. It was also referred to by the *Golden Mirror of Medicine* (*Yi Zong Jin Jian*, 医宗金鉴), which summarized the condition as basically due to Wind, Damp and Heat (99).

3.3.2 She shi (蛇虱)

In the Ming Dynasty, Wang Kentang included the term She shi in his *Standards of Pattern/Syndrome Identification and Treatment* (*Zheng Zhi Zhun Sheng*, 证治准绳). It had white scales after being scratched which were painless but itchy (99).

3.3.3 Bai bi (白疕)

Bai bi (白疕) was firstly described in *Complete Compendium of Surgery* (*Wai Ke Da Cheng*, 外科大成) by Qi Kun in the Qing dynasty. It has become the current standard TCM term for psoriasis. It was caused by Wind invading the skin and the blood being too dry to nourish the skin (100). It was described as like a scab that was white and itching, and could develop to white scales after being scratched. Also it was often called *She shi* (蛇虱) (99).

3.3.4 Bai ke chuang (白壳疮)

In the Ming Dynasty, Sheng Douyuan included this disorder in his *Disclosure of External Medicine Mystique* (*Wai Ke Qi Xuan*, 外科启玄). It spread over the full body and was white, painless and itching. The *Dong Tian Ao Zhi* (洞天奥旨) also described its clinical manifestation as being mainly on both upper limbs, or on the trunk when it called Wan xuan (Stubborn psoriasis, 顽癣) (99).

3.3.5 Song pi xuan (松皮癣)

This disorder was so named as the scales frequently itched and showed red/white spots mixed like in pine bark. There were similar descriptions of these symptoms in *Golden Mirror of Medicine* (*Yi Zong Jin Jian*, 医宗金鉴), In this book, the condition was thought to be mostly related to Wind and also partially to Dry blood (98). Both Song pi xuan and Bai bi are regarded as the disease descriptions most similar to psoriasis by most contemporary TCM practitioners (100).

3.3.6 Ying qian feng (银钱疯)

The name was recorded in *Completed Works at Feng Meng* (*Feng Meng Quan Shu*, 疯门全书) by Xiao Xiaoting in the Qing Dynasty. The lesion was like a coin, red on the inside while

white on the outside. If you pierce it there is no blood but it is white like silver, first it is on the body and then on the face (99).

3.4 The TCM etiology of psoriasis

In terms of the etiology of psoriasis in TCM thought, there has been a progressive change in the way the disease has been viewed. Prior to the Sui-Tang period, the emphasis was on external pathogens such as Wind, Cold, Dampness, Heat, etc. (see Maciocia (101) for an explanation of the meanings of these terms in TCM). During the Ming-Qing era, internal damage was considered to be an important aspect of the condition, and there was a focus on the involvement of blood (*xue fen*). The following is a brief outline of the etiology of psoriasis according to TCM.

3.4.1 External pathogens

Wind-dampness located at the level of the skin and flesh can induce psoriasis. In addition, Cold-dampness can stagnate the flow of qi and blood, which can result in the disease. This viewpoint that these external pathogens contributed to psoriasis was stated in *Treatise on the Pathogenesis and Manifestations of All Diseases* (*Zhu Bin Yuan Hou Lun*, 诸病源候论), and was followed by many medical books in the Tang dynasty and Song dynasty (99, 100).

Since Fire (Heat) came to be regarded as the primary pathogen during the Jin dynasty and Yuan dynasty (1115-1368), this pathogen was thought to relate to psoriasis. In this view, Heat toxin invading the lung can result in the disease. This point was made in *Yan Yong He's Comprehensive Medical Book* (*Yan Yong He Yi Xue Quan Shu*, 严用和医学全书) (100).

3.4.2 Internal damage

Disorders of blood such as Blood-dryness and Blood-heat can facilitate the invasion of external pathogens such as wind pathogen into the body. The lung channel and spleen channel adversely affected by Blood-dryness and Wind-toxin, and this can eventually lead to psoriasis. *Orthodox Manual of External Medicine* (*Wai Ke Zheng Zong*, 外科正宗) was the first text to state that psoriasis is closely related to disorders of the lung channel and spleen

channel (100).

Long-term Blood-deficiency can induce internal wind which when combined with external dryness adversely impacts the nourishment of the skin and flesh. As a result, psoriasis could occur in the coming autumn. This school of thought was presented in *Complete Works of Pattern/Syndrome Identification and Treatment* (*Wai Ke Zheng Zhi Quan Shu*, 外科证治全书) (99).

In summary, the main external pathogen is Wind, which together with the pathogens of Cold, Dampness, Dryness and Fire toxin can result in psoriasis. In general, psoriasis is closely related to the condition of the blood. Blood-dryness, Blood-heat, and Blood-deficiency form the basic underlying causes of psoriasis. Blood-heat or Blood-dryness may lead to Blood-stasis. Blood-stasis is a condition that usually lingers inside the body for long term, and this is the main factor that leads to the protracted nature of psoriasis (99).

3.5 The TCM physiology and pathology of psoriasis

In the physiology and pathology of psoriasis, the functions of the internal organs as well as the regulation of qi and blood are involved. In short, psoriasis mainly depends on the physical functions of the lung, heart, liver and blood.

3.5.1 The physiology and pathology of lung in TCM

According to the concept that the ‘lung regulates the skin and (body) hair’, the skin is closely related to the lung. The essence of water and food is distributed to the body by the lung and this essence nourishes the skin and (body) hair to keep it shiny. In addition, the Defense qi (wei qi) is also diffused outward to the skin by the lung. Defense qi can fulfill the three physical functions: skin warming, helping the skin prevent the invasion of external pathogens, and controlling the opening and closing of the pores. When there is lung deficiency and non-diffusion of defense qi, external pathogens easily invade the body. When the lung channel is affected, there can be wheals, papules, erythema, scaly dry skin, itching, dry nose and throat, or dry cough without phlegm (102).

3.5.2 Physiology and pathology of heart in TCM

Fire and Heat can induce all pain, itch, sores and ulcers. The heart regulates Fire, so the above conditions are related to the heart. When there is Heat in the heart the colour of the network vessels (i.e. fine blood vessels) changes to red. Also wind can enter the network vessels, and as a result there is erythema. In addition, when there is Heat in the blood this induces Wind which intensifies leading to Dryness and the production of the white scales (103).

3.5.3 Physiology and pathology of liver in TCM

Liver regulates free coursing of the qi and the storing of the blood. When its function of free coursing is normal, there is fluent movement of qi and blood as well as normal emotional states. However, when there is abnormal emotion without free coursing, this may lead to an abnormal qi dynamic. When liver fails in its free coursing function Fire can be generated. Lesions can be induced or aggravated when fire it produced in this way. In addition, Lung yin can be impacted by the Fire reducing fluid, which results in a dry throat. Liver fire can lead to dysfunction of the lung defense system producing abnormal opening and closing of the pores. Therefore so psoriasis patients become prone to catching colds. Furthermore, Cold can also inhibit the liver function of free coursing. Therefore, upper respiratory tract infections and psychological factors constitute the main inducements to relapses or aggravations in psoriasis (104).

3.5.4 Physiology and pathology of blood in TCM

The skin is an important organ in maintaining the close relationship between the flow of qi and blood throughout the body. Also, the growth and metabolism of the skin depend on the function of qi, blood, and body fluids (jin ye) (102). For psoriasis, TCM considers that the principal factor is blood while the secondary aspects are Wind, Heat and Dryness. In general, this disease starts as Blood heat which is followed by Blood deficiency, then Blood dryness and Blood cold. Blood toxin appears when there are abnormal developments of the disease.

Blood stasis is present throughout the entire progress. Therefore, the methods of Quickening the blood and Dispelling stasis are applied in the all the types of psoriasis (105).

3.5.5 The pathogenesis of psoriasis in TCM

Chinese medicine considers psoriasis to be mainly induced by Blood heat. This may manifest in a variety of ways: Constitutional Blood heat combined with external pathogens such as wind heat or wind cold; Long-term-stagnation heat induced by disturbed emotional states plus stagnant *qi*; Stagnated heat due to *qi* dysfunction and spleen-stomach disharmony from excessive intake of stimulating foods; or Exuberant Heat stirring up wind resulting from Heat pathogens congesting the Construction-defense (ying wei) system.

After the disease has lasted for a long time, the Blood heat gradually lessens but the condition of the blood is impaired. This leads to more severe Blood-stasis and to wind-dryness. This condition can also be induced by Blood deficiency and the skin losing nutrition as can occur in some gynaecological disorders. When there is Exuberant fire toxin and qi and blood are both ablaze as a result of Heat toxin not being resolved, severe symptoms such as erythema and desquamation may occur all over the body (106).

3.6 The TCM diagnosis of psoriasis

3.6.1 Clinical symptoms and syndromes in TCM

In psoriasis, the presenting symptoms are various. Yu *et al* 2013, analysed 369 published papers on case reports, and collected 598 symptoms which were classified into 226 standardized symptoms. These were in the following four clusters: skin lesions, systemic symptoms (excluding tongue and blood vessels), tongue appearance and pulse manifestation. The highly frequent symptoms (>60%) were in the first two clusters with skin lesion forming the most frequent cluster (38.68%). They reported that Blood heat and Fluids insufficiency constituted the main pathogenic features of psoriasis (107):

Skin lesions: Of 35 symptoms, 5 symptoms appeared frequently (frequency ≥ 100) and 15 symptoms appeared commonly (10 ≤ frequency < 100). The frequent symptoms included: erythema, scale, itch, infiltration hypertrophy and blood spots. The first two symptoms were the most highly frequent and appeared in over 50% of the skin lesions. Erythema included bright red lesions, dark red lesion, newly-appearing lesions with expansion of existing lesion area, light red skin, guttate lesions, refractory lesions, plaque lesions, rapidly-aggravating lesions, and squamiform lesions. The scales included thick scales, many scales, caduceus scales, tightly-adhesive scales and silvery scales.

Systemic symptoms (excluding tongue and blood vessels): These involved 104 symptoms that related to the skin, consciousness, appearance, taste, sleep, temperature, pain, sweating, excretion, and reproduction. 8 symptoms frequently appeared (frequency ≥ 100) and 33 appeared commonly (10 ≤ frequency < 100). The eight symptoms were dark urine, dry mouth, upset feeling, dry excretion, thirstiness, constipation, irritability, dry throat, and dry skin.

Tongue appearance: This aspect included the tongue color, tongue shape, tongue condition, tongue coating (coating color and coating nature), etc. Eleven features frequently occurred (frequency ≥ 100): red tongue, yellow tongue fur, thin tongue fur, white tongue fur, dark tongue, petechial tongue, greasy tongue fur, scanty tongue fur, purple tongue, and pale tongue.

Pulse manifestation: seven kinds of pulse frequently occurred (frequency ≥ 100): fine pulse, rapid pulse, string-like pulse, slippery pulse, sunken pulse, moderate pulse, and rough pulse (107).

3.6.2 The TCM syndromes seen in psoriasis

The TCM syndromes that manifest in psoriasis are various. There are more than 50 different syndromes described for psoriasis. These can be broadly divided into syndromes based on the characteristics of the disease and syndromes based on the method of syndrome differentiation used in TCM. In the former group, the syndromes can be based on

pathogenesis (i.e. constitution, emotions, external pathogens, dietary factors), the various patterns of manifestation of the disease (i.e. psoriasis vulgaris, pustular psoriasis, arthritic type, erythroderma pattern), the different features of the lesions (i.e. erythema, scale, pustule, erosion) and the stage of the disease (i.e. active, stationary and regressive). In the latter group, there are multiple TCM syndrome differentiation methods (108). The main TCM syndromes are described below.

Li and Qu 2010 conducted a study on the distribution of TCM syndromes in 205 psoriasis patients. The main syndromes consisted of Blood heat, Blood heat plus blood stasis, Blood stasis, Blood heat plus blood dryness, and Blood stasis plus blood dryness. Blood heat plus blood stasis was the most frequent, and 90.2% of the sample was accounted for by this syndrome and two additional syndromes (Blood heat and Blood heat plus blood dryness). This indicated that Blood heat was the main factor in the pathogenesis of this disease. Over 40% patients had the following six accompanying syndromes: Damp heat, Heat toxin, Cold and heat, Depressed liver and Yin deficiency, while there were no accompanying syndromes in the remaining patients. The disease can be aggravated by the accompanying syndrome at certain times. And Cold and heat was the most frequent among them. In the active stage, the main syndromes that appeared were Blood heat and Blood heat plus blood stasis, and there was also Blood heat plus blood dryness. In the stationary stage, there was Blood heat plus blood stasis, Blood heat and Blood heat plus blood dryness of which the main syndrome was Blood dryness (109).

In another multi-site study with 600 psoriasis patients, Deng *et al* 2006 found that 78.0% were stable in term of their TCM syndrome while 22.0% belonged to the non-stable category. Blood heat, Blood dryness and Blood stasis occurred in 98.9% of the stable psoriasis patients, who accounted for 77.2% of the sample size. In particular, Blood heat was the most frequent among all syndromes, and was present in around one third of the sample. The distribution of syndromes was closely related to the disease stage. Blood heat primarily appeared in the active stage, Blood dryness mainly occurred in the regressive stage and Blood stasis often appeared in the stationary stage (110).

The main syndromes of psoriasis are Blood heat and/or Blood stasis, so the methods Clearing heat and draining fire, or Quickening the blood and dispelling stasis are commonly applied in the management of psoriasis.

3.6.3 Contemporary TCM diagnostic criteria in psoriasis

In psoriasis, there are numerous TCM syndromes referred to in the literature but in the official guidelines on the number of syndromes are considerably fewer. The diagnostic criteria for *Bai Bi* (白疕) are specified in section 3 of chapter 14 in *Clinical research guidelines on Chinese medicinal herbs (Trials)* (中药新药临床研究指导原则(试行)) (111). This guideline was issued by the China State Drug Administration, which provides the regulatory policies and scientific principles and methods that should be applied in clinical research. This section referred to the textbook *Traditional Chinese External Medicine* (中医外科学) (edition in 1997) and *National Standards of The People's Republic of China – TCM Clinical Diagnosis and Treatment Terminology* (中华人民共和国国家标准·中医临床诊疗术语) (111). The following syndromes were specified in the guidelines as follows:

1) Wind heat syndrome

Primary Symptoms: raised lesions mainly with papules and maculopapules, lesion base is bright red, spotting blood after scale removal, and possible isomorphic reaction.

Secondary Symptoms: lesions in remission or relapse stages, probably with itch at different severity levels, emotional upset, thirst or dry mouth, constipation, yellow urine, red tongue, yellow tongue fur, and rapid pulse.

2) Blood deficiency syndrome

Primary Symptoms: lesions mainly in patches, pale lesion base, large-sized but thin scales.

Secondary Symptoms: long term course of disease, probably with itch, fatigue, pale tongue, thin white tongue fur, and fine pulse.

3) Blood stasis syndrome

Primary Symptoms: thick lesions with induration, dark red lesion base, and hard to remove scales.

Secondary Symptoms: long term course of the disease, persistent lesions, possible itch at different levels of severity, no remarkable systemic symptoms, dark or petechial tongue, and rough or fine-rough pulse.

A syndrome diagnosis can be established based on at least 2 symptoms of the primary symptoms and 2 of the secondary symptoms (111).

3.7 TCM management of psoriasis

In Traditional Chinese Medicine, the management of psoriasis includes a variety of treatment approaches and therapies of which Chinese herbal medicine (CHM) is frequently applied. The internal administration of CHM is mainly used in more severe patients, with large lesion area, for rapidly progressing symptoms, long term disease course, or complicated cases. External CHM is usually applied for milder cases or uncomplicated conditions.

Treatment based on syndrome differentiation (TSD) is frequently used in the management of psoriasis using internal CHM via decoction. In this approach the selection of herbal formula is based on the presenting syndrome and is modified according to the individual case according to the severity and the primary symptoms. Another approach is the use of a CHM preparation that is specific for the disease (PSD) which is widely applied in the internal and external management of psoriasis throughout the healthcare system by TCM practitioners and conventional clinicians including dermatologists.

A variety of CHM preparations are employed including pills, tablets, granules, liquid solutions, ointments, creams, tinctures, thin gels, bath formulae, steaming formulae, etc. Some of these CHMs have been manufactured into Chinese patent medicines for clinical

application. In addition, acupuncture and the other remedies also play a role in the management of psoriasis.

3.7.1 Treatment based on syndrome differentiation (TSD) and the relevant schools

This approach can be divided into a number of contemporary schools of thought regarding the TCM management of psoriasis. In a review that included 123 studies of psoriasis treatment using the TSD approach, 116 studies based their syndrome differentiation approach on qi-blood and/or fluids (particularly on blood), 4 based their approach on the internal organs involved, and 3 took a different approach. The most highly frequent syndromes are listed below together with the Treatment principle, which is a statement of the objectives of the CHM and the names of the herbs most commonly used in the CHM formula for psoriasis patients who conform to each syndrome (112):

1) Blood heat syndrome (n=100):

Treatment principle: to clear heat and resolve toxins, cool blood and quicken blood.

Formula ingredients: Huang qin (and/or Huang bai, Da huang, Huang lian, Shi gao, Qing dai), Tu fu ling (and/or Jin yin hua, Bai hua she she cao, Ban lan gen, Lian qiao, Da qing ye), Sheng di (and/or Chi shao, Mu dan pi, Zi cao, Xuan shen, Shui niu jiao), Dan shen (and/or Ji xue teng, Hong hua, E zhu, Tao ren, San leng).

Modifications: for removing cold, add Fang feng (and/or Chan tui, Jing jie, Jiang can, Qin jiu, Ling yang jiao); for removing dampness, add Bai xian pi, Ku shen, Di fu zi, Yi yi ren, Cang zhu, and/or Fu ling (112).

2) Blood dryness syndrome (n=84):

Treatment principle: to nourish blood, remove cold and moisten dryness.

Formula ingredients: Dang gui (and/or He shou wu, Bai shao, Shu di huang), Fang feng (and/or Chan tui, Jing jie, Jiang can, Qin jiu, Ling yang jiao), Mai dong (and/or Tian dong,

Huang jing, Sha shen) (112).

3) Blood stasis syndrome (n=62):

Treatment principle: to clear heat and resolve toxin, quicken blood and transform stasis.

Formula ingredients: Huang qin (and/or Huang bai, Da huang, Huang lian, Shi gao, Qing dai), Tu fu ling (and/or Jin yin hua, Bai hua she she cao, Ban lan gen, Lian qiao, Da qing ye), Dan shen (and/or Ji xue teng, Hong hua, E zhu, Tao ren, San leng), Wu shao she (and/or Quan jie, Feng fang, Wu gong, Di long, Chuan shan jia).

Modifications: for moving qi, add Chuan xiong (and/or Chen pi, Chai hu, Zhi ke, Ru xian, Mo yao) (112).

Main Schools of thought in the TSD approach to psoriasis

The TSD approach to the management of psoriasis has greatly developed during the last century and has assimilated some of the advances derived from Western Medicine. A number of TCM schools of thought in psoriasis have gradually built up based on the expertise of prestigious practitioners of TCM, such as Zhao Bin-nan, Zhu Ren-kang, Jin Qi-feng, Zhang Zhi-li, Gu Bo-hua, Ma Shao-yao, Qin Wan-zhang, Ouyang Heng, and Xuan Guo-wei (105, 113-120). Amongst these experts, proponents of the Blood heat approach include Zhao Bin-nan, Zhu Ren-kang, Jin Qi-feng, Zhang Zhi-li and Gu Bo-hua while Ma Shao-yao and Xuan Guo-wei also focused on Blood stasis, Qin Wan-zhang was concerned with other aspects of Blood in addition to heat and stasis, and the focus of Ouyang Heng's approach was on Blood heat and its relationship with the condition of the qi and body fluids (105, 113-120).

The main features of the approaches of these experts, their main treatment principles and typical treatments are outlined in Table 3.1. It should be noted that in clinical practice these formulas can be modified according the individual's constitution, response and the stage of the disease.

Table 3.1 Traditional Chinese Medicine schools of thought in the syndrome differentiation of psoriasis

Expert: **School**	**Syndrome**	**Treatment principles**	**Primary formula,** **Ingredients**	**Reference**
Zhao Bin-nan: Blood heat	blood heat	clearing heat, cooling blood, quickening blood	Liang Xue Huo Xue Tang Sheng huai hua, Bai mao gen, Sheng di, Chi shao, Dan shen, Zi cao gen, Ji xue teng	Shi 2009
	blood dryness	nourishing blood, resolving toxin	Yang Xue Jie Du Tang Dang gui, Dan shen, Tu fu ling, Feng fang, Wei ling xian	
Zhu Ren-kang: Blood heat	blood heat & wind dryness	clearing heat & resolving toxin	Ke Yin Yi Fang Tu fu ling, Ren dong teng, Cao he che, Bai xian pi, Bai dou gen, Ban lan gen, Wei ling xian, Sheng gan cao	Li 1985
	blood deficiency & wind dryness	enriching yin, nourishing blood, moistening dryness	Ke Yin Er Fang Sheng di, Dan shen, Yuan shen, Ma ren, Da qing ye, Bai dou gen, Bai xian pi, Cao he che, Lian qiao	
Jin Qi-feng: Blood heat	blood heat	cooling blood, clearing heat, extinguishing wind	Kuai Lan Liang Xue Tang Ban lan gen, Sheng kuai hua, Zhao xiu, Bai hua she she cao, Zi cao, Sheng di, Chi shao, Ku shen, Bai xian pi, Tu fu ling, Quan jie, Jiang can	Jin 1989
	dampness heat	clearing heat, cooling blood, resolving toxin	Long Zhao Xie Shi Tang Long dan cao, Chao shan zhi, Yan huang bai, Zhao xiu, Yin hua, Chi shao, Sheng yi ren, Ku shen, Bai xian pi, Di fu zi, Tu fu ling, Ze xie	

	blood dryness	enriching yin, moistening dryness, clearing heat, removing wind, quickening blood, transforming stasis	Zeng Ye Jie Du Tang Sheng di, Yuan shen, Mai dong, Da qing ye, Bai hua she she cao, Sheng kuai hua, Dang gui, Dan shen, Bai xian pi, Qi she, Ling xian	
Zhang Zhi-li: Blood heat	blood heat	clearing heat, cooling blood, quickening blood	Liang Xue Huo Xue Tang (Bai Bi Yi Hao) Ling yang jiao feng, Sheng gan cao, Zi cao gen, Chi shao, Xuan shen, Shu jun, Gan sheng di, Sheng kuai hua, Da qing ye, Bai xian pi, Ci ji li, Bai mao gen	Wang 2007
	blood dryness	nourishing blood, enriching yin, moistening skin	Yang Xue Jie Du Tang (Bai Bi Er Hao) Tian dong, Mai dong, Dang gui, Dan shen, Xuan shen, Lu feng fang, Ji xue teng, Sheng di, Bai mao gen, Tu fu ling, Bai xian pi	
	blood stasis	quickening blood, dissipating stasis	Huo Xue San Yu Tang (Bai Bi San Hao) San leng, E zhu, Tao ren, Hong hua, Dan shen, Ji xue teng, Gui jian yu, Chi shao, Dan pi, Sheng yi yi ren, Tu fu ling, Ban lan gen	
Gu Bo-hua: Blood heat	wind cold	effusing sweat & resolving flesh, harmonizing construction & defence (ying-wei),nourishing blood & regulating blood	Gui Zhi Tang plus Si Wu Tang modification Sheng jiang, Gui zhi, Shao yao, Da zao, Gan cao, Dang gui, Shu di, Chuan xiong	Gu 1977
	blood heat	cooling blood, clearing heat, removing toxin	Xi Jiao Di Huang Tang modification Xi jiao, Sheng di, Shao yao, Dan pi	
	blood stasis	nourishing blood, quickening blood	Tao Hong Si Wu Tang modification Shu di, Dang gui, Bai shao, Chuan xiong, Tao ren, Hong hua, Zhen zhu mu, Mu li, Ci shi	

Ma Shao-yao: Blood stasis & heat toxin	blood heat	cooling blood, clearing heat, resolving toxin	NS Sheng di, Chi shao, Zi cao, Shui niu jiao, Da qing ye, Bai hua she she cao, Dan shen, Tao ren, Sheng gan cao, etc.	Ma 1999
	blood stasis	quickening blood, dissipating stasis, resolving toxin	NS Dan shen, San leng, E zhu, Hu zhang, Hong teng, Sheng gan cao, et.	
Qin Wan-zhang: Regulating blood	blood heat	clearing heat, cooling blood	NS Mu dan pi, Shan zhi, Jin yin hua, Sheng di, Da qing ye, Chi shao, Hong teng, Ban lan gen, etc.	Qin 2008
	blood dryness	nourishing yin, moistening dryness	NS Bai shao, He shou wu, Huang jing, Ji xue teng, Sheng di, Xuan shen, Tian dong, Mai dong, Zhi mu, Yu zhu, Xiao hu jiao, etc.	
	blood deficiency	nourishing blood, moistening dryness	NS Shu di huang, Huang qi, Dan shen, Zhi shou wu, Ji xue teng, Wu shao she, Dang gui, Zhi gan cao, etc.	
	blood stasis	quickening blood, dissipating stasis	NS San leng, E zhu, Liu yue xue, Lang du, Dan shen, Ru xian, Mo yao, Tao ren, Hong hua, etc.	
	blood cold	warming blood, dissipating cold	NS Gui zhi, Ma huang, Dang gui, Chi shao, Zhi chuan wu, Ji xue teng, Fu zi, Xi xin, Tong cao, Huang teng, etc.	
	blood toxin	clearing & resolving blood toxin	NS Huang lian, Sheng shan zhi, Mu dan pi, Sheng di, Xi jiao, Ling yang jiao, Huang teng, Qing dai, Sheng cao, Zi cao, Zi hua di ding, Tu da huang, etc.	

Ouyang Heng: Blood heat & qi-fluids detriment	blood heat & yin detriment (vulgaris)	clearing heat & resolving toxin, boosting qi & nourishing yin	Zhu Huang Tang I Huang lian, Zhu ye, Shi gao, Dang shen, Mai dong, Huang quan, Zhi zi, Huang bai, Shui niu jiao, San qi, Lou lu.	Xiang 2008
	blood heat & repression (vulgaris)	coursing liver & resolving toxin, clearing heat & nourishing yin	Zhu Huang Tang II Lou lu, Chai hu, Huang lian, Huang qin, Huang bai, Zhi zi, Dang shen, Mai dong, Sheng shi gao, Zhu ye, Sheng di huang, Dang gui, Bai shao	
	toxin stasis (vulgaris)	clearing heat & resolving toxin quickening blood & dissipating stasis	Xian fang huo ming yin plus Lou Lu Jin yin hua, Lou lu, Ru xian, Mo yao, Dang gui wei, Chi shao, Tian hua fen, Zhe bei mu, Chuan shan jia, Zao jiao, Gan cao, Fang feng, Bai zhi, Chen pi.	
	blood deficiency & wind dryness (vulgaris)	nourishing blood & quickening blood, enriching yin & moistening dryness	NS Sheng di huang, Mu dan pi, Xuan shen, Dan shen, Bai shao, Ma ren, Shan dou gen, Ku shen, etc.	
	critical fever stage (pustular type)	clearing heat & draining fire	Liang Xue Jie Du Tang modified Dan gui, Sheng di huang, Niu bang zi, Hong hua, Mu tong, Chi shao, Mu dan pi, Lian qiao, Jie geng, Qing dai, Zi cao, Xi yang shen, Xuan shen, etc.	
	paracmastic fever stage (pustular type)	clearing & resolving remaining toxin, boosting qi & nourishing yin	Zhu Ye Shi Gao Tang, Huang Lian Jie Du Tang plus modified Yu Nv Jian Zhu ye, Shi gao, Ban xia, Mai meng dong, Ren shen, Gan cao, Jing mi, Huang lian, Huang qin, Huang bai, Zhi zi, Shi gao, Shu di huang, Zhi mu, Niu xi.	
	stable recovery stage (pustular type)	enriching stomach yin	Yi Wei Tang, Zeng Ye Tang plus Xi yang shen Sha shen, Mai dong, Bing tang, Xi sheng di, Yu zhu, Xuan shen, Xi yang shen.	

Xuan Guo-wei: Blood heat & blood stasis	blood heat	clearing heat	NS, Primary ingredients: Tu fu ling, Bai hua she she cao, Ban lan gen, Da qing ye, Di fu zi, Ban bian lian, Bai xian pi, Lu feng fang, Chuan xiong, Ze xie, Che qian cao, Gan cao, Shan dou gen, Sheng da huang, Sheng di huang, Mu dan pi, Zi cao, Chi shao, Shui niu jiao.	Cha 2006
	blood deficiency	dispelling wind	NS, Primary ingredients: Tu fu ling, Bai hua she she cao, Ban lan gen, Da qing ye, Di fu zi, Ban bian lian, Bai xian pi, Lu feng fang, Chuan xiong, Ze xie, Che qian cao, Gan cao, Dan shen, Ji xue teng, Xuan shen, Sha shen Mai dong.	
	blood stasis	quickening blood	NS, Primary ingredients: Tu fu ling, Bai hua she she cao, Ban lan gen, Da qing ye, Di fu zi, Ban bian lian, Bai xian pi, Lu feng fang, Chuan xiong, Ze xie, Che qian cao, Gan cao, Dan shen, San leng, E zhu, Wang bu liu xing.	

3.7.2 The approach that uses CHM preparations that are specific for the disease (PSD)

While syndrome differentiation is commonly used to select a CHM for a particular patient, another common approach is the use CHM preparations that are specific for the disease (PSD). This approach is also typically used in Western medicine and in herbal medicine in other countries. When this approach is used, the CHM is not modified according to the signs and symptoms, rather, a standardised medicine is used. This approach is often used in the external management of psoriasis.

Compared to TSD, the PSD approach is convenient to prescribe in the clinic and is widely applied. In addition, it is well suited to the requirements of the contemporary clinical trial particularly when using a RCT study design.

There are a variety of standardised CHM treatments for the management of psoriasis. The following are examples of commonly used internal and external CHMs (106):

1) Internal management:

***Ke yin* pill**: for Blood heat and excessive wind, 1 pill in orally, twice daily.

Compound *Qing dai* capsule: for Blood heat and excessive wind, 4 capsules orally, twice daily.

***Leigongteng Duo Dai* tablet**: mainly for the arthritic type, pustular type and erythroderma type. Also used with caution for psoriasis vulgaris. Recommended dose: 60-80 mg daily divided into 2-3 oral administrations.

***Leigongteng* tablet:** mainly for the arthritic type, pustular type and erythroderma type. Also used with caution for psoriasis vulgaris. Recommended dose: 6 tablets daily divided into 2-3 oral administrations.

2) External management:

Herbal Bath: can use for all types but use with caution in acute cases. *Chu tao ye* and *Ce bai ye* each 250g are decocted in 5,000ml for 20 minutes. Bathe in the warm filtered decoction 2-3 times weekly.

Herbal ointment: for all types. *Huanglian* ointment, *Jia Wei Huanglian* ointment, or *Heidou Liuyou* ointment is externally applied on the affected surface, 2-3 times daily.

There have been numerous clinical trials of the PSD approach for psoriasis. A number of these trials are included in the systematic reviews in Chapters 5 and 6.

3.7.3 Acupuncture and the other manual therapies

Acupuncture and other manual therapies including cupping, moxibustion, point injection and catgut embedding can be used singly and in combination. The focus of these treatments is removing wind and relieving itch. In addition, the following treatment principles can be used in acupuncture treatment: nourishing blood and moistening dryness, quickening blood and dissipating stasis, and clearing heat and cooling blood. The Selection of acupuncture points can be based on the syndrome differentiation (TSD) approach or upon the lesion location. These approaches are summarized in Table 3.2 (121).

Table 3.2 Approaches to acupoint selection for the management of psoriasis

Prescription characteristic	**Syndrome/condition: treatment principles**	**Selected acupoints**
Based on syndrome differentiation	Wind heat & blood dryness: cooling heat, clearing blood & dispelling wind	Feng chi (Gb-20), He gu (LI-4), Da zhui (Du-14), Tao dao (Du-13), Qu chi (LI-11), Xue hai (Sp-10), etc.
	Blood deficiency & wind dryness: nourishing blood, harmonizing blood, dispelling wind & moistening dryness	Zu san li (St-36), San yin jiao (Sp-6), Xue hai (Sp-10), Ge shu (Bl-17), Tai xi (Kd-3), Feng chi (Gb-20), He gu (LI-4), etc.

	skin-flesh stasis: quickening blood & dissipating stasis	He gu (LI-4), Tai chong (Liv-3), San yin jiao (Sp-6), Nei guan (Pc-6), Xue hai (Sp-10), Ge shu (Bl-17), etc.
Based on lesion location	NS	Governing vessel points, or Hua tuo jia ji points (M-BW-35) according to the relevant the disposable nerve segment of the skin

As regards the efficacy of acupuncture treatment, it is more effective for psoriasis vulgaris than for the other types and acute types respond better than chronic types. In general, the efficacy of treatment depends upon the disease course with those in the remission stage responding better than those with actively progressing disease while response is least when the disease is in a stationary stage (121). However, a blinded RCT of 56 patients with long-standing plaque psoriasis reported that although PASI scores declined in both the active and sham acupuncture groups after 10 weeks of treatment, there was no significant difference between groups (122).

In terms of its antipruritic effect, the following mechanisms of acupuncture action have been proposed. One possible mechanism is acupuncture can reduce or counteract nerve impulses to the spinal cord by its stimulation of the local area. Also, acupuncture may inhibit proteases and affect local bradykinin generation. Acupuncture possibly affects the spinal cord and the sensory area of the brain to relieve itch (121). A review of studies on acupuncture for itch reported that experimental studies have shown acupuncture to reduce histamine-induced itch and it can also exert antipruritic effects. It appears to act via interference in central and peripheral itch transmission (123). In a cross-over study of 14 participants with atopic dermatitis, the efficacy of real versus sham acupuncture was investigated using self-report and functional magnetic resonance imaging (MRI). The results showed that the real acupuncture produced significant reductions in itch and there were significant changes in the MRI. Particularly, acupuncture inhibited itch and itch-evoked activation involving the insula, putamen, and premotor and prefrontal cortical areas (124).

However, acupuncture may not always be beneficial in psoriasis, since exogenous stimulation by acupuncture might also induce the skin sensory nerve endings to release neuropeptides, which could lead to neurogenic inflammation. In addition, considering the

isomorphic reaction (aka. Kobner's phenomenon) which can occur in psoriasis, there is controversy regarding whether acupuncture should be used near local psoriatic lesions (125).

Numerous experimental studies into the actions of various CHMs in psoriasis have been conducted in the last twenty years. These are discussed in Chapter 7.

Chapter 4: Methodology for systematic reviews of clinical trials of herbal medicine for psoriasis

4.1 Aims

The aim of this component of the thesis is to undertake systematic reviews of controlled clinical trials of herbal medicine (HM) for psoriasis. Trials could be published in English or Chinese or Japanese and available electronically via major databases.

The databases selected for searching were as follows:

- Medline via Pubmed (September 2012);
- Cochrane Library via Wiley InterScience (September 2012);
- Embase (September 2012);
- China National Knowledge Infrastructure (CNKI) (中国知网) (September 2012); and
- Chinese Scientific Journals Full Text Database (CQVIP) (维普网) (September 2012).

These were searched from their inception to September 2012 with no limits being placed on publication type, date, language etc. An additional identification by searching reference list was supplemented.

The methodology used for the searches was based on that recommended in The Cochrane Handbook of Systematic Reviews (126). The results of the electronic searches were supplemented by examining reference lists in retrieved articles. Searches of clinical trial registries and hand searches of journals were not undertaken.

4.2 Selection of search terms and search procedure

The search terms consist of three components:

- Clinical condition,
- Intervention, and
- Study style.

In the selection of search terms related to psoriasis, reference was made to the Cochrane Skin Group via http://skin.cochrane.org, and a published Cochrane review protocol on psoriasis (53, 127). For terms relating to study design the Cochrane library website: http://www.thecochranelibrary.com/view/0/index.html, and other Cochrane reviews were consulted (80, 128). For terms related to HM, reference was made to another Cochrane review protocol (53).

The terms identified from the above procedure were supplemented by examining lists of MESH terms in PubMed, lists of Source and Map Terms in Embase and lists of search terms in other systematic reviews (36, 42).

Separate lists of search terms were developed for PubMed, Embase and Cochrane Library. These had minor differences according to the characteristics of the search functions employed by the particular database. Search terms were further refined by undertaking trial searches and terms that were inclusive of others and consequently redundant were removed from the list. Nevertheless, since the aim of the searches was to be as comprehensive as possible, a broad range of terms was included. For CNKI and CQVIP the search interfaces are considerably different from those of the English language databases. These search methods are detailed below.

Each of the sets of search terms is presented below.

4.2.1 Embase

The Embase search terms were divided into three main groups: 1. Clinical condition, 2. Intervention, and 3. Study type. These were further divided into subgroups to facilitate searching. The three main groups were combined with 'AND', and terms within a group were linked with the Boolean operator 'OR' (see Fig. 4.1).

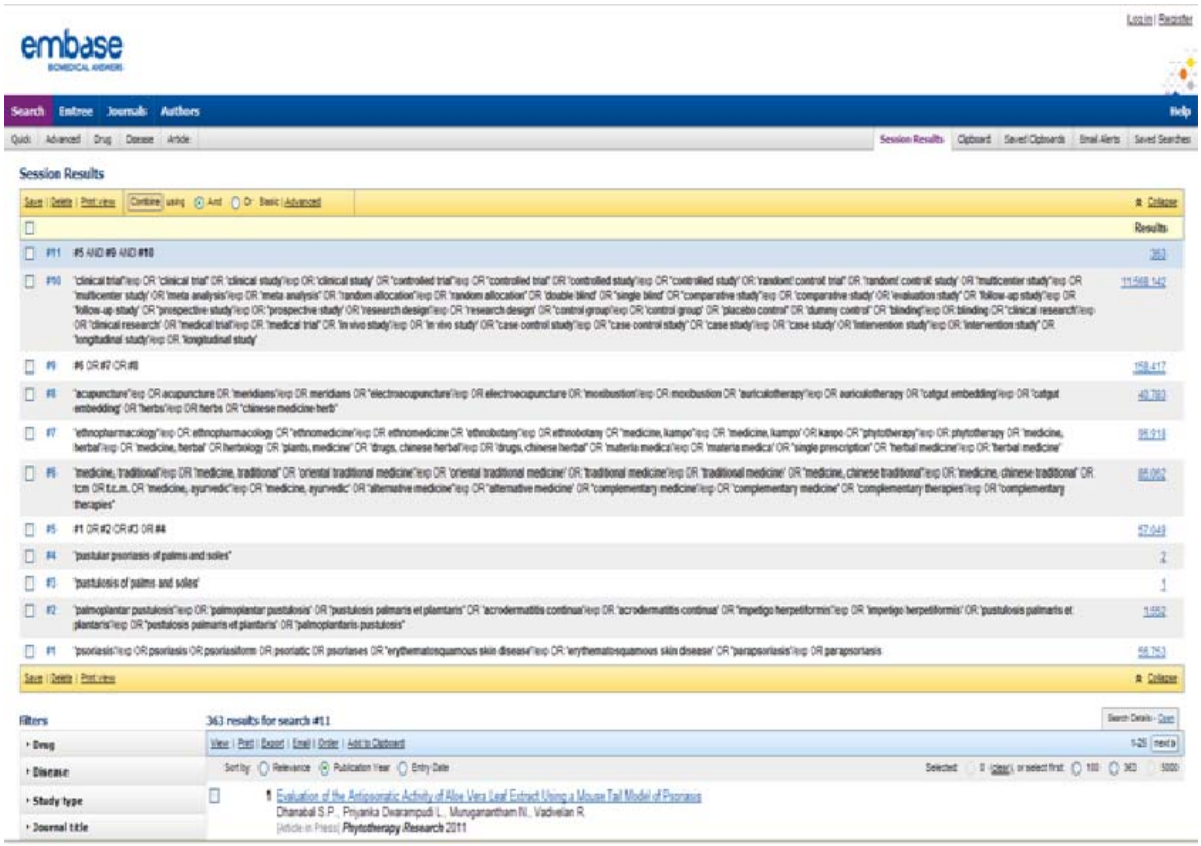


Fig. 4.1: Groups of search terms in Embase

Finally the three main groups of search terms were linked with the operator 'AND' to obtain a result for all references which satisfied the three groups of terms. The terms used for Embase are listed below:

I. Clinical condition

a) psoriasis OR psoriasiform OR psoriatic OR psoriases OR 'erythematosquamous skin disease' OR parapsoriasis
b) 'palmoplantar pustulosis' OR 'Pustulosis Palmaris et Plamtaris' OR 'Acrodermatitis Continua' OR 'Impetigo Herpetiformis' OR 'Pustulosis Palmaris et Plantaris' OR 'Palmoplantaris Pustulosis'
c) 'Pustulosis of Palms and Soles'
d) 'Pustular Psoriasis of Palms and Soles'

Ⅱ. Intervention

a) 'Medicine, Traditional' OR 'oriental traditional medicine' OR 'traditional medicine' OR 'Medicine, Chinese Traditional' OR TCM OR T.C.M. OR 'Medicine, Ayurvedic' OR 'Alternative Medicine' OR 'Complementary Medicine' OR 'Complementary Therapies'
b) Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR 'Medicine, Kampo' OR Kanpo OR Phytotherapy OR 'Medicine, Herbal' OR Herbology OR 'Plants, Medicine' OR 'Drugs, Chinese Herbal' OR 'Materia Medica' OR 'Single Prescription' OR 'Herbal Medicine'
c) Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR 'Catgut embedding' OR Herbs OR 'Chinese Medicine Herb'

Ⅲ. Study type

'Clinical Trial' OR 'clinical study' OR 'Controlled Trial' OR 'Controlled study' OR 'random! control! Trial' OR 'random! control! Study' OR 'Multicenter Study' OR Meta-Analysis OR 'random allocation' OR double-blind OR single-blind OR 'comparative study' OR 'evaluation study' OR 'follow-up study' OR 'prospective study' OR 'research design' OR 'control group' OR 'placebo control' OR 'dummy control' OR blinding OR 'clinical research' OR 'medical trial' OR 'in vivo study' OR 'case control study' OR 'case study' OR 'intervention study' OR 'longitudinal study'

The results of the search were downloaded to a dedicated Endnote library using the 'Export Citation(s)' function in Embase and the 'Complete Reference' option.

4.2.2 Medline via Pubmed

PubMed was searched via http://www.ncbi.nlm.nih.gov/pubmed using the PubMed Advanced Search webpage. The three main groups of search terms are listed below:

I. Clinical condition

Psoriasis OR psoriases OR psoriasiform OR parapsoriasis OR Psoriasis, Arthritic OR Skin Diseases, Papulosquamous OR palmoplantar pustulosis OR Pustular Psoriasis of Palms and Soles OR Pustulosis Palmaris et Plantaris OR Pustulosis of Palms and Soles OR

Acrodermatitis Continua OR Impetigo Herpetiformis OR Psoriatic Erythroderma OR Pustulosis Palmaris et Plamtaris OR psoriatic Dermatitis OR Palmoplantaris Pustulosis OR Arthritis, Psoriatic OR Psoriasis Arthropathica

Ⅱ. Intervention

Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR T.C.M. OR Medicine, Ayurvedic OR Alternative Medicine OR Complementary Medicine OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparations OR Plant Extracts OR Plants, Medicine OR Materia Medica OR Single Prescription OR Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR Catgut embedding OR Herbs OR Chinese Medicine Herb OR Herbal Medicine

Ⅲ. Study type

Clinical Trial OR clinical study OR biomedical research OR Controlled Trial OR Controlled study OR random* control* Trial OR random* control* study OR Multicenter Study OR Meta-Analysis OR random allocation OR double-blind OR single-blind OR comparative study OR evaluation study OR follow-up study OR prospective study OR research design OR control group OR blinding OR clinical research OR medical trial OR in vivo study OR case control study OR case study OR intervention study OR longitudinal study OR Clinical Trial OR Randomized Controlled Trial OR placebo OR control OR random OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw])

The three main groups were combined with ‘AND’ and the results downloaded to a dedicated Endnote library.

4.2.3 Cochrane Library

The Cochrane Library was accessed at http://www.thecochranelibrary.com via Wiley InterScience using the ‘advanced search’ page.

Since the focus of the Cochrane library is clinical trials and systematic reviews of clinical trials the group of search term for ‘study type’ was not used for this search. The two groups and subgroups of terms are listed below:

I. Clinical condition

Psoriasis OR psoriases OR psoriasiform OR parapsoriasis OR psoriatic OR "Skin Diseases, Papulosquamous" OR "palmoplantar pustulosis" OR "Pustular Psoriasis of Palms and Soles" OR "Pustulosis Palmaris et Plamtaris"

Ⅱ. Intervention

a) "Chinese Medicine, Traditional" OR "Medicine, Chinese Traditional" OR "Chinese Traditional Medicine" OR "Traditional Chinese Medicine" OR "Medicine, Traditional" OR "Medicine, Oriental Traditional" OR "Medicine, Chinese Traditional" OR TCM OR T.C.M. OR "Medicine, Tibetan Traditional" OR "Medicine, Mongolian Traditional" OR "Medicine, East Asian Traditional" OR "Alternative Medicine" OR "Complementary Medicine" OR "Complementary Therapies" OR "Medicine, Ayurvedic"

b) "Chinese Drugs, Plant" OR "Drugs, Chinese Herbal" OR "Chinese Herbal Drugs" OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR "Medicine, Kampo" OR Kanpo OR Phytotherapy OR "Medicine, Herbal" OR Herbology OR "Plants, Medicinal" OR "Plant Preparations" OR "Plant Extracts" OR "Materia Medica" OR "Single Prescription" OR Herbs OR "Herbal Medicine"

c) Acupuncture OR "Acupuncture Therapy" OR "Therapy, Acupuncture" OR "Acupuncture Points" OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR "Acupuncture, Ear" OR "Auricular Acupuncture" OR "Catgut embedding"

The subgroups of group 2 were combined with ‘OR’ then groups 1 and 2 were combined with ‘AND’. The sub-databases for ‘Clinical trials’ and ‘Cochrane Reviews’ were searched and the results were downloaded to a dedicated Endnote library.

4.2.4 CNKI (中国知网)

CNKI (中国知网) is a mainstream Chinese database. It can be accessed via its home page at

http://www.cnki.net by registering and logging in. It is advisable to access the New Version Publishing Platform (新版出版平台) for the improved interface. Furthermore, the Head Database of Chinese Academic Literature Net Publication (中国学术文献网络出版总库) can be accessed, which provides the Advanced Search (高级检索) option.

The search terms were designed in three components: Clinical condition, Intervention and Study type. Each component was formed of a number of core words, such as 中医药 *Zhong yi yao* (Chinese medical pharmacopoeia). These terms will link to lists of additional relevant terms which appear in a pop-up window when you click a specific button on the Advanced Search webpage of CNKI (中国知网). These additional terms can then be further selected (See Fig. 4.2).

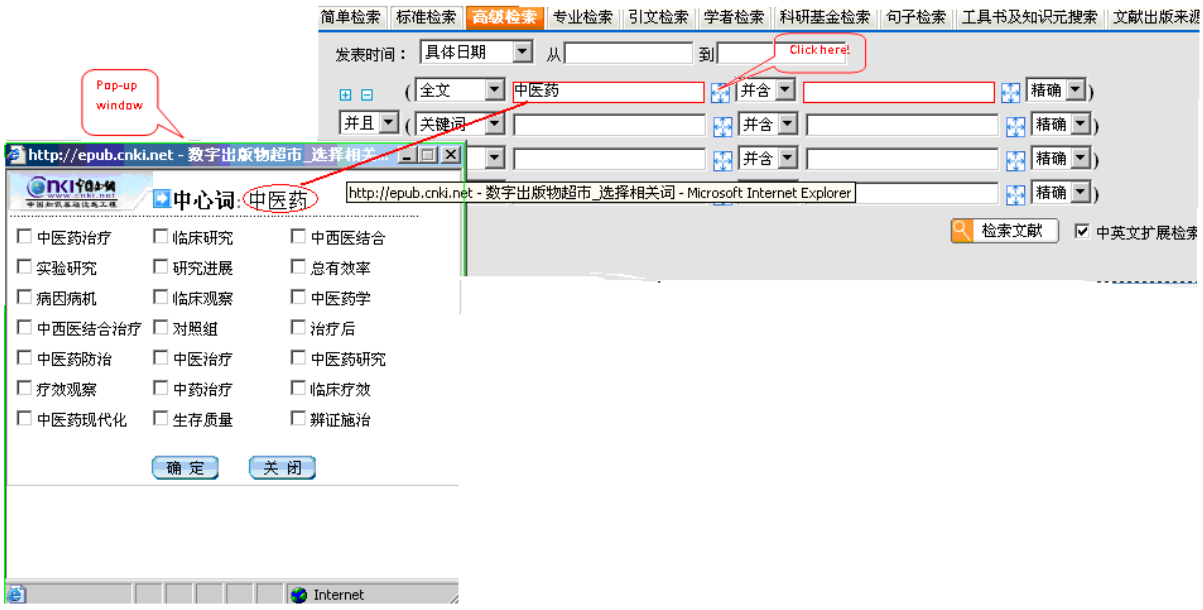


Fig. 4.2 The selection of search terms using the CNKI Advanced Search interface

Using this approach, most search terms were determined. For clinical condition, some search terms were selected from the specialized books, such as 中药大辞典 *Zhong Yao Da Ci Dian* (index section) (129)and reference was made to 中医大辞典 *Zhong Yi Da Ci Dian* to identify whether they matched the description of psoriasis (130). There is a space limitation in the CNKI search interface so up to 14 terms can be used. Therefore the search terms for intervention were divided into three sub-groups: Ⅱ-a, Ⅱ-b and Ⅱ-c. The search terms are as follows:

I. Clinical condition

银屑病 牛皮癣 白疕 白庇 疕风 庇风 干癣 白秧 顽癣 疥癣 蛇虱 松皮癣 银钱疯 白壳疮

Ⅱ. Intervention

a) 中医 中医治疗 中医临床 中医辨证 中医干预 祖国医学 辨证施治 中西医 中西医学 中西医结合 中西医治疗 中西医结合治疗 中西医结合疗法 中西医结合方法

b) 草药 中草药 中医药 中医药学 中医中药 中药治疗 中医药治疗 中医药疗法 中医药防治 中医药研究 中医中药治疗 中草药治疗应用 耳针 耳穴

c) 针灸 针灸治疗 针刺治疗 针灸疗法 针灸临床 传统医学 传统医药 传统治疗 中国传统医学 替代疗法 替代医学 替代治疗 补充和替代医学 保守治疗

Ⅲ. Study type

随机临床观察 随机临床试验 临床随机研究 临床随机试验 临床观察 临床研究 临床疗效 随机试验 疗效观察

4.2.5 CQVIP（维普网）

CQVIP（维普网）at http:www.cqvip.com is an important retrieval platform for Chinese literature. It originated as The Title Database of Chinese Scientific Journals (中文科技期刊篇名数据库), became kown as the Chinese Scientific Journal Database (中文科技期刊数据库) and its current formal title is Chongqing Weipu Zixunwang 重庆维普资讯网. We usually commence to retrieve literature by clicking the Advance Search (高级检索) button on top right corner of the home page after registering and logging in to an account.

The search terms were again designed in three components: Clinical condition, Intervention and Study type. Each component comprised a number of Key Words (关键词) and potential synonyms were identified as follows. Enter the key word, such as 银屑病 *Ying xie bing* (psoriasis), in the text box under the Search Term (检索词) label, then select the indistinct

(模糊) setting from the drop-down list, and then click on the Search Synonym (查看同义词) button. A new page appears with a list of synonyms which can be selected (see Fig. 4.3).

Fig. 4.3: The development of CQVIP search terms using synonyms

In this manner, most of the search terms were determined. Regarding clinical condition, some terms were selected from specialized books, such as 中药大辞典 *Zhong Yao Da Ci Dian* (index section) (129), and by reference to 中医大辞典 *Zhong Yi Da Ci Dian* (130) to identify whether they matched the description of psoriasis.

Considering that quite a few potential search terms overlapped entirely with the other terms, a Boolean Formula was applied to identify those terms that will be discarded for further searching, for example, if A NOT B = 0, then A should be included in B. In the first two lines of the Advanced Search (高级检索) web page, set NOT (不包含) and Title/ Key Word (题名或关键词). In the two text boxes under Search Term (检索词), enter the narrowly defined term(s) and then the broader term in the box below. Then click the Search (检索) button (See Fig. 4.4). Note that the Boolean operators: OR, AND, NOT are correspondingly represented by the symbols: +, *, - in the CQVIP search fields. However, in general, the logical sequence in the CQVIP advanced search follows the input order rather than the Boolean logical priority.

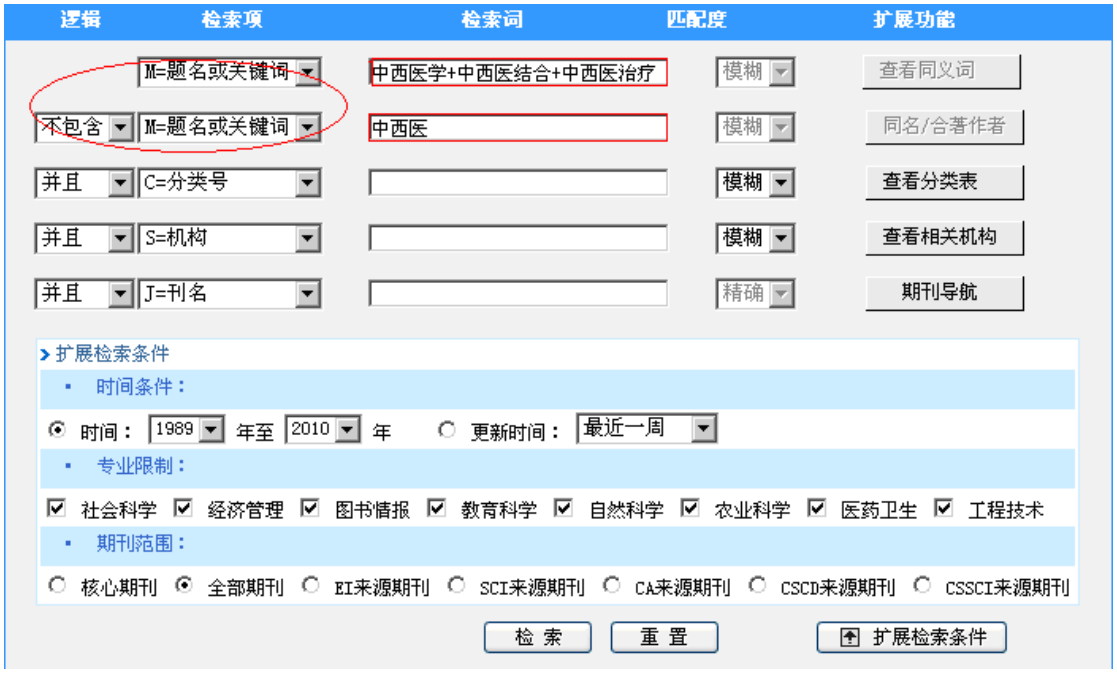


Fig. 4.4: The refinement of CQVIP search terms using NOT

The resultant refined search terms are as follows:

I. Clinical condition

银屑病+牛皮癣+松皮癣+疥癣+疥癣病+白庀+白庇+庀风+庇风+干癣+白秕+顽癣+蛇虱+银钱疯+白壳疮+白疮

Ⅱ. Intervention

a) 中医+祖国医学+传统医学+传统医药+传统治疗+替代疗法+替代医学+替代治疗+补充和替代医学+保守治疗+保守疗法+汉医+汉方医学+东医+中西医+中西药

b) 草药+中草药+中医药+中医中药+中药治疗+调理+证侯+证治+辨证施治+辨病论治+辨证论治+辨证用药+辨证治疗+辨症施治

c) 针灸+针刺+体针+新针疗法+刺灸+刺络放血+刺络疗法+三棱针法+耳针+耳穴+耳压

Ⅲ. Study type

随机+疗效+临床观察+临床研究+临床试验+临床监测

4.3 Removal of duplicates

The results of each database search were saved in separate Endnote libraries. The results of the three English language databases were then combined into a single library and the 'discard duplicates' function was used to remove duplicate citations. The combined Endnote library was then scanned item by item to identify any other duplicate citations. These were subsequently removed to arrive at a total number of different citations identified by the three searches.

A similar procedure was undertaken for the two Chinese language databases. After the duplicates had been removed in this Endnote library, the combined Endnote libraries for the English and Chinese language databases were cross referenced to identify studies that appeared in both. These were removed from the total search results.

An additional process for identification was searching reference lists. This was applied to review articles and RCTs. When additional articles were located these were added to the combined Endnote library.

4.4 Screening and categorization of citations

A series of categorisation criteria were developed to assist in the screening of the citations. These are listed in the following chapter. Each of the citations in the Endnote library, which includes the title and in most cases the abstract, was read by the researcher (SD) and it was allocated a category, for example C1 'not related to psoriasis' or C4. '*in vitro* study (e.g. cell culture)'. All citations that made reference to a clinical study in humans or a review of clinical studies were identified and full text articles were obtained. A second researcher independently scanned and checked the categories allocated in the Endnote library (BM). Any discrepancies were discussed and modifications made if required. A third person (TZ) was available to resolve any disputations. This was not required.

Based on the full text, clinical studies were divided into sub-categories. Case-series and other uncontrolled studies were not considered in this review.

For the articles reporting controlled clinical trials in humans, data on study design, treatment and control intervention was extracted into an Excel spread sheet to facilitate further

selection and evaluation of the suitability of the study for inclusion in the review. Data checking was carried out by BM and/or Xuedong An (another PhD candidate).

4.5 Exclusion and inclusion criteria

The languages of the included studies were limited to English, Chinese and Japanese.

Studies that included a CAM treatment intervention other than herbal medicine (internal and/or external) were excluded. Herbal medicine was broadly defined to include plant-derived medicinal material excluding purified compounds.

Studies that used a combination of HM plus ultraviolet radiation therapy in the intervention arm were excluded. However, studies combining HM and anti-psoriatic pharmacotherapy (APP) were included. APP did not include phototherapy or photochemotherapy, and can include but was not limited to: emollients, corticosteroids, vitamin D3 analogues, tazarotene, coal tar, dithranol, methotrexate (MTX), ciclosporin, retinoids, fumarates and/or biologicals (131). Studies that used a form of pharmacotherapy not related to anti-psoriatic pharmacotherapy were not included.

Those studies that applied psychological or stress reduction techniques such as meditation, music therapy, hypnosis were not included. Manual therapies including acupuncture were excluded. Therapies based on baths and/or climate such as Dead Sea Cure were also not included. Vitamin and/or mineral therapies, homoeopathy, fish oils and other animal oils were not included but studies that employed a multi-ingredient herbal medicine that included a vitamin, mineral and/or animal oil in addition to the HM were not excluded. Also included were herb-based studies in which a vitamin, mineral and/or animal oil was added as an adjunctive ingredient such as an excipient or preservative.

Studies that did not employ randomisation, or claim to have employed randomisation, in the allocation of participants were excluded from further evaluation. Study designs that did not use placebo or a standard APP therapy as a control were excluded. Also, designs that compared psoriasis sufferers with a normal control were excluded.

Consequently, the included studies were randomised controlled trials, with or without blinding, that compared the HM therapy with a placebo, conventional pharmacotherapy or no treatment. The intervention could be an internal/oral or external/topical method.

Therefore the systematic reviews were divided into internal/oral herbal medicines and external/topical HMs on order to ensure valid comparisons.

The stages in the exclusion and inclusion process were presented as a flowcharts according to the PRISMA guidelines (132).

4.6 Data extraction

For the clinical trials not excluded under the above criteria, detailed data were extracted to an Excel spread sheet. These included the number, age and gender of study participants; duration of the study and follow-up; dosage of medications; outcome measures etc. See the individual characteristics of the studies details in the following chapters on the systematic review (Chapters 5 & 6).

4.7 Evaluation of the Methodological Quality of the Studies

The methodological quality of the studies was evaluated using the 'Risk of Bias Table' developed by the Cochrane Collaboration (133). Two researchers assessed Risk of Bias according the methods, SD, Xuedong An and BM. Any disagreements were discussed and resolved with recourse to a third person (Dr Yanyi Wang) if agreement could not be reached.

4.8 Data analysis

In cases where two or more studies employing similar designs and used the same outcome measures, the results were pooled and meta-analyses undertaken using RevMan 5.1. For continuous data Weighted Mean Difference (WMD) was used and Relative Risk (RR) was used for dichotomous data. A fixed effect-model or random effect-model was selected depending upon the level of heterogeneity (134). Heterogeneity was assessed using I^2. Sensitivity analyses were used to explore sources of heterogeneity. When ten or more comparable studies were identified, publication bias was explored using a Funnel Plot.

In order to ensure the meaningfulness of meta-analyses, studies were grouped where possible according to design, intervention, comparator and outcome measure. Studies of topically applied HMs and orally/systemically applied were considered separately.

When multi-ingredient herbal formulae were used, analyses were undertaken to determine the most frequently applied herbs. Where possible, sensitivity analyses were used to explore the effects of formulae that shared ingredients in common.

The safety of the HMs was explored based on the incidence of adverse events (AEs) reported in the clinical studies and whether there were any serious adverse event (SAE).

In order to determine how the herbs might function in the management of psoriasis and its associated symptoms, further analyses were undertaken of the main herbs used in the clinical trials. The methods and results for these analyses are presented in subsequent chapters. The method and results for the analysis of the experimental studies is presented in Chapter 7 and the method and results for the analysis of the therapeutic targets and biological pathways analysis is presented in Chapter 8.

Chapter 5: Results of systematic review of RCTs on internal HM for psoriasis

This chapter presents the results of a systematic review of randomised controlled trials (RCTs) of herbal medicines (HMs) for psoriaisis. The methodology was reported in Chapter 4. The overall search results are reported below following by the systematic review of HMs used internally. The results reported in this chapter have been published (135). The reviews of HMs used externally/topically are presented in Chapter 6.

5.1.1 Overall results of searches of databases

The search results for the databases are shown individually below followed by the combined results for all searches. These are the consolidated search results for all of the following systematic reviews in Chapters 5 and 6.

The numbers are given for the initial search conducted on 2011.10.5 and the update search on 2012.9.12.

5.1.1.1 PubMed

Initial search (2011.10.5)

Group 1 Condition = 43,671

Group 2 Intervention = 402,781

Group 3 Study type = 7,911,235

Combined 1 AND 2 AND 3 = 422

Additional citations retrieved at search update (2012.9.12) = 32

Total = 454

References were downloaded to a separate Endnote library.

5.1.1.2 Cochrane library

Initial search (retrieved on 2011.10.5)

Group 1 Condition = 2,898

Group 2 Intervention = 14,021

Combined 1 AND 2 = 40

Additions from updated search (2012.9.12)= 0

Total = 40

References were downloaded to a separate Endnote library.

5.1.1.3 Embase

Initial search (retrieved on 2011.10.5)

Group 1 Condition = 57,049

Group 2 Intervention = 158,417

Group 3 Study type = 11,568,142

Combined 1 AND 2 AND 3 = 361 (after discarding 22 duplicated hits)

Additions from updated search (2012.9.12) = 17

Total = 378

References were downloaded to a separate Endnote library.

5.1.1.4 CQVIP (initial search on 2011.10.7, updated on 2012.9.12)

Due to the limitations of the database, the search terms for Intervention were separated into three components (a, b, c) and each group was combined with the other groups of terms: Intervention a AND Condition AND Study type etc. Results were downloaded to an

Endnote library. Finally, 485 hits were located after removing 23 duplications. 40 additional entries were derived from the update of 2012.9.12. The total number of retrieved citations was 525.

5.1.1.5 CNKI (retrieved on 2011.10.10, updated on 2012.9.12)

Initial search (retrieved on 2011.10.5)

a) Stage Ⅰ:

Step 1 Condition (Ⅰ) = 20,108

Step 2 Combined 1 AND Intervention (Ⅱ-a) = 1,464

Step 3 Combined 2 AND Study type (Ⅲ) = 368 and downloaded to Endnote library 1

b) Stage Ⅱ:

Step 4 Condition (Ⅰ) = 20,108

Step 5Combined 4 AND Intervention (Ⅱ-b) = 950

Step 6 Combined 5 AND Study type (Ⅲ) = 249 and downloaded to Endnote library 2

c) Stage Ⅲ:

Step 7 Condition (Ⅰ) = 20,108

Step 8 Combined 7 AND Intervention (Ⅱ-c) = 168

Step 9 Combined 8 AND Study type (Ⅲ) = 50 and downloaded to Endnote library 3

d) Stage IV:

Step 10 Combined 3 Endnote libraries into a new Endnote library 4 = 579 (after discarding 88 duplicated hits).

Additions from updated search (2012.9.12) = 44

Total = 623

5.1.2 Combination of database retrievals:

a) The five databases searches were combined into a new Endnote library. After duplicate removal the total number of citations = 1,583
b) Additional citations based on reference lists = 31
c) Number of citations in combined Endnote library after filtration = 1,614

5.1.3 Screening:

Hit categorisation and exclusion based on condition, intervention or language

Screening the 1,614 entries in the Endnote library resulted in the following numbers of entries for each of the categories (see Table 5.1). The categories defined as exclusion criteria are marked 'E 1-10' in Table 5.1. Almost 30% entries were related to disorders other than psoriasis or were not related to a form of CAM treatment. A small number (n=16) were not in English, Chinese or Japanese.

Table 5.1 Results for categorisation criteria:

Categorisation criterion	**N.**	**Total N.**	**%**
C1. not related to the searched disorder eg psoriasis – E1	259	x	16.05
C2. not related to CAM (Complementary & Alternative medicine including Traditional Medicine)-E 2	200	x	12.39
C3. not in the specified languages: eg Chinese, English, Japanese, German- E3	16	x	0.99
E1-E3: Combined	x	475	29.43
C4. in-vitro study (e.g. cell culture)-E4	31	x	1.92
C5. in-vivo study (i.e. animal study)- E4	27	x	1.67
C6. physiological study in humans- E4	3	x	0.19
C7. review of non-clinical studies- E4	28	x	1.74
E4: Combined	x	89	5.51
C8. Systematic review: Other CAM-E6	5	x	0.31
C9. General review: Other CAM- E6	19	x	1.18
C10. Systematic review: Other Herbal Medicine (HM)- E6	1	x	0.06
C11. General review: Other HM- E6	11	x	0.68
C12. Systematic review: TCM- E6	22	x	1.36

C13. General review: TCM- E6	56	x	3.47
C14. Discussion on TCM theory, diagnosis, differentiation etc.- E6	40	x	2.49
E6: Combined	x	154	9.54
C15.UV: Other CAM-E9	37	x	2.29
C15. CT: Other CAM-E9	2	x	0.12
C15r. RCT: Other CAM- E9	22	x	1.36
C18. CT: TCM – Acupuncture, Tui Na-E9	5	x	0.31
C18r. RCT: TCM – Acupuncture, Tui Na-E9	27	x	1.67
C19. CT: TCM – other-E9	4	x	0.25
E9: Combined	x	97	6.01
C16. CT: Other HM-E10	2	x	0.12
C17. CT: TCM – HM-E10	85	x	5.27
E10: Combined- CTs (HM)/Non-RCTs	x	87	5.39
C16r. RCT: Other HM-RCTs	4	x	0.25
C17r. CT: TCM – HM-RCTs	296	x	18.34
RCTs (HM): Combined	x	300	18.59
C20. Uncontrolled study: Other CAM-E8	15	x	0.93
C21 Uncontrolled study: Other HM-E8	2	x	0.12
C22 Uncontrolled study: TCM – HM only-E8	297	x	18.40
C23 Uncontrolled study: TCM – Acupuncture, Tui Na-E8	42	x	2.60
C24 Uncontrolled study: TCM – other-E8	1	x	0.06
E8: Combined	x	357	22.12
C25 Adverse event report, toxicology – general (inc other CAM)-E7	5	x	0.31
C26 Adverse event report, toxicology – TCM-E7	19	x	1.18
C27 Chemical analysis – Other HM-E7	0	x	0
C28 Chemical analysis – TCM-E7	4	x	0.25
E7: Combined	x	28	1.74
C29 Epidemiology, economic studies etc: WM and general-E 5	8	x	0.50
C30 Epidemiology, economic studies etc: CAM-E5	19	x	1.18
E5: Combined	x	27	1.67
Total:	1614	x	100

5.1.4 Evaluation for eligibility:

Of the 27 entries that were epidemiological and/or economic studies, most related to CAM. 89 entries were for experimental studies and other entries rot related to clinical trials, and a further 28 were adverse event reports, chemical analyses or toxicological reports of relevance to herbal medicine.

The remaining 995 entries were for clinical studies or reviews of CAM therapies for psoriasis. These were further assessed on the basis of the full text articles. Of these entries, 154 were reviews of at least one form of CAM. One article (136) reported results for one uncontrolled clinical study and two controlled clinical studies, so this study was evaluated further as a controlled clinical study. The references for uncontrolled clinical studies accounted for 357 entries leaving 484 references for controlled clinical trials of a CAM therapy.

5.1.5 Evaluation of controlled clinical trials for inclusion:

5.1.5.1 Exclusions based on the intervention (E 9)

Of the 484 controlled clinical trials, 97 were excluded because they used a CAM therapy other than herbal medicine, physical therapy, or phototherapy. These included eleven studies employing psychological or stress reduction techniques such as meditation, music therapy, or hypnosis (137-147), and 32 studies that applied manual treatments such as acupuncture and/or reflex therapy. One study investigated seal oil for psoriatic arthritis (148) and one was of fish oil (149). Two studies involved the extract from sweet whey (150, 151). One related to climatic treatment in the Dead Sea (152). Eight studies involved physical therapy such as Spa baths, Laser Therapy, Ozone autohemotherapy (79, 81, 83, 84, 90, 153-155). Four studies used compounds purified from plants (77, 78, 82, 85). Another 37 studies used CAM combined with phototherapy/ photo-chemotherapy. The above 97 studies were excluded.

5.1.5.2 Exclusion of the non-randomisation studies (E 10)

Of the 387 remaining controlled studies (CTs), 87 studies did not use randomisation in the allocation of the subjects, or did not include a definite randomisation statement in their study methodology. These were not included in this systematic review on randomised trials. One study (156), that did report randomisation, investigated a range of skin disorders including psoriasis but did not report separate data for psoriasis, so it was excluded.

5.1.5.3 Exclusions based on trial design (E 11)

Since the aim of the reviews was to investigate the efficacy of herbal medicines for psoriasis, with a particular focus on the pharmaceutical actions of the HM(s), the design of the

included trials had to be sufficient to allow a direct comparison between the HM and a placebo or a pharmaceutical intervention with known effect.

There were a variety of study designs among the 300 identified studies. In total, 96 studies compared different HM treatments (i.e. HM vs HM) with no comparison with a placebo, a no treatment group or a conventional pharmaceutical therapy or phototherapy. Ten studies compared HM Medicine with combination care using HM plus WM (HM vs HM + WM) and 18 studies used complex designs with mixed HM interventions (internal and external) that did not allow clear assessment of the actions of one of the intervention. In addition, 21 studies did not involve a clear comparison in the study design, for example one group included a combination of a herbal medicine plus a Western medicine while the comparator was a different Western medicine (HM 1 + WM 1 vs WM 2).

Psoriasis vulgaris or plaque psoriasis was not definitely diagnosed in 5 studies. 42 studies did not state the primary outcome measures, or provide their results. Also, 69 studies applied a conventional therapy other than an anti-psoriatic pharmacotherapy (APP) as the comparator. Therefore these 261 studies did not meet the above inclusion criteria and were excluded.

5.1.6 Summary of the candidate entries for eligibility

The included entries were further divided into two domains: 1. studies that used herbal medicine taken internally as the main intervention; and 2. studies that used herbal medicine administered externally as the main intervention. There were 11 studies in the first domain that are included in this chapter (results published in (135)); and 29 studies the second domain (2 RCTs were reported in one article), which will be separately reported in Chapter 6 which includes three SRs (157-159).

5.2 Systematic review 1: Herbal Medicine in the internal management of psoriasis: efficacy, safety and pharmacological actions of the main herbs

5.2.1 Introduction

For moderate to severe psoriasis, internal management is often primary clinical solution. Currently unwanted side effects resulting from the long-term application of internally used anti-psoriatic pharmacotherapies (APP) remains an issue (35). Complementary and

alternative medicine (CAM), including HM, is used by about 50% of psoriasis patients in America and Europe, often in conjunction with conventional treatments (54, 160-162). So an evaluation of its efficacy and safety is of relevance to physicians and patients. A number of reviews have examined the use of HM for psoriasis, but these did not focus upon its internal or oral use (35, 36, 48, 49, 157, 163-166).

This systematic review focuses on controlled clinical trials of the efficacy and safety of oral herbal medicines (HM) in the management of psoriasis vulgaris. All included studies compared the HM with an oral placebo or conventional anti-psoriatic pharmacotherapy (APP) with Psoriasis Area Severity Index (PASI) as an outcome measurement. In addition, this review aims to identify individual herbs that show promise of efficacy and examine the experimental evidence for activities of relevance to psoriasis in order to identify possible directions for drug discovery and drug development (167).

5.2.2 Method

The major biomedicine databases: EMBASE, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Chinese Scientific Journals Full Text Database (CQVIP) were searched from their respective inceptions to September 2012. Three groups of search terms were employed: 1. Clinical condition (psoriasis etc.); 2. Intervention (herbal medicine etc.); and 3. Study type (controlled trial etc.). Terms were adjusted for different databases. Review articles were identified and their reference lists were searched (see Chapter 4 for details).

The HM interventions could include the oral administration of single or multiple HMs or extracts thereof. HMs were classified as natural products of plant origin but multi-ingredient formulations could also include natural products of animal or mineral origin, vitamins, and excipients. Isolated bioactive compounds, homoeopathic formulations, mineral therapies, and specific vitamin remedies were not included. APPs could include: emollients, corticosteroids, vitamin D3 analogues, tazarotene, coal tar, dithranol, methotrexate (MTX), ciclosporin, retinoids, fumarates and/or biologicals (131). Phototherapy was not included.

Comparisons were between HM used internally and internal placebo or internal APP. Topical co-interventions that were used in both arms of the study were allowed. Comparisons between two HMs and comparisons that combined an internal HM with an

APP were not included.

Psoriasis vulgaris, presenting as plaque psoriasis, is the most common type of psoriasis. In order to enable valid data pooling, only studies that included participants who had been diagnosed with this type of psoriasis were included.

In general, internal treatments are typically prescribed based on the amount of body surface area involved (168) and are mainly applied in moderate to severe conditions to control the disease adequately (169) while external remedies are applicable for mild psoriasis (65). Psoriasis Area Severity Index (PASI) can be used to assess psoriasis severity in moderate to severe conditions and is a well validated and sufficiently detailed measure (170). To ensure comparability between studies, only those that included PASI as an outcome measure were included. Studies that included mixed psoriasis phenotypes or did not report the type of psoriasis were excluded.

Two researchers conducted searches, extracted data, and assessed Risk of Bias according the methods specified by the Cochrane collaboration (171). Any disagreement was resolved by discussion with another colleague if agreement could not be reached (see Chapter 4 for details). Fig. 5.1 presents a flowchart of study selection process.

Data were analysed in RevMan 5.1 as Relative Risk (RR) or Mean Difference (MD) with 95% confidence intervals (95% CI) using fixed or random-effect models depending upon heterogeneity (172). A 50% reduction of PASI score (PASI 50) was selected as the criterion for a clinically effective response in the meta-analyses (173).

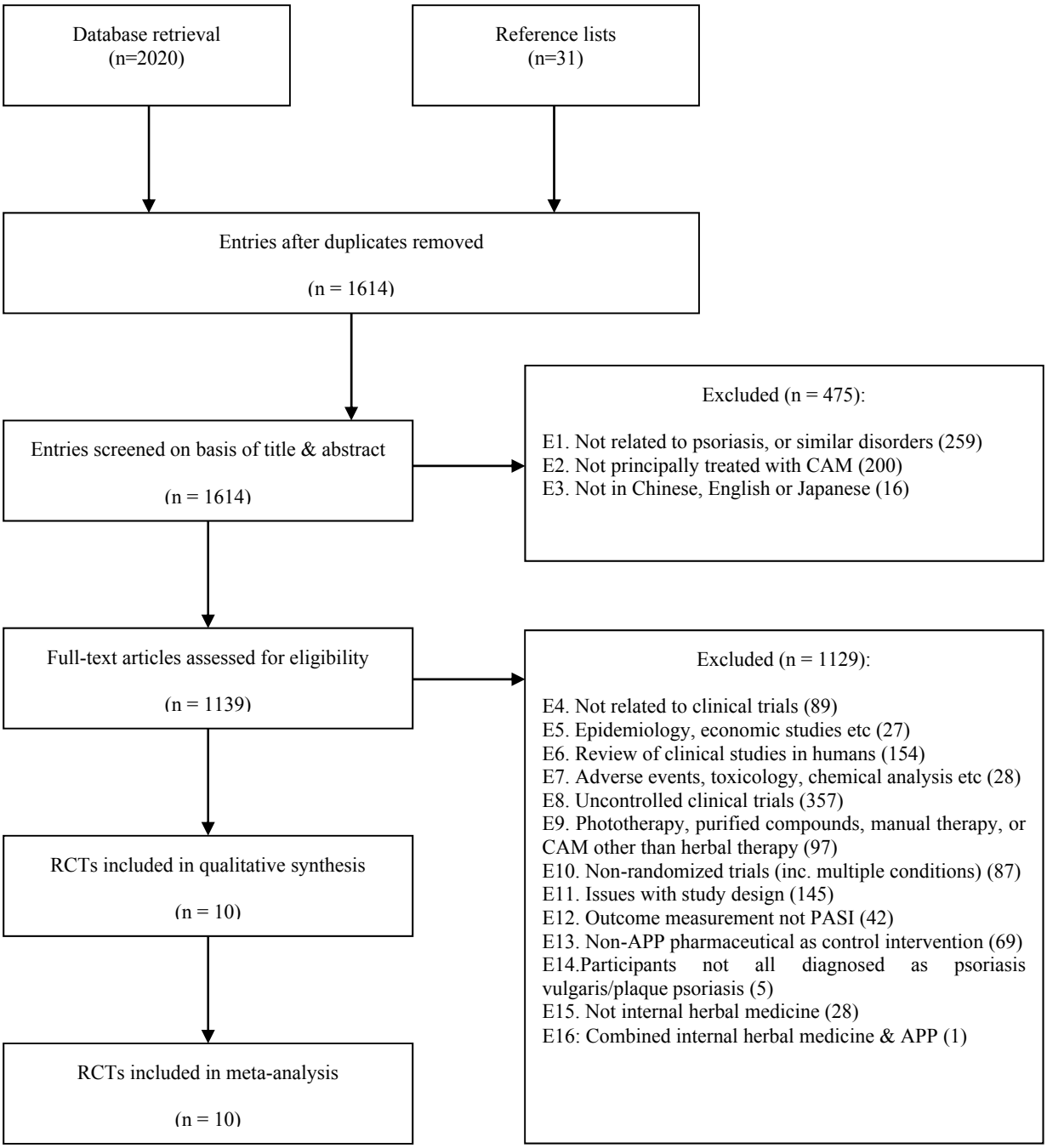


Fig. 5.1 Flow chart of selection of randomised controlled trials (RCTs) of internal herbal medicine for psoriasis [adapted from Deng 2013 (135)].

5.2.3 Results

2,020 entries were retrieved from the databases and 31 studies from reference lists. After removing duplicates, the remaining 1,614 entries were screened and full-texts obtained of 1,139 articles. Ten studies met the inclusion criteria (174-183).

9 studies were conducted in China and one was conducted in India. Eight were published in Chinese and the remaining two were published in English. In total, 658 patients completed the ten included studies (Table 5.2). The largest study was of 105 participants (174) and the smallest was of 50 participants (177). Study duration ranged from 4 weeks (1 study) (181) to 6 months (1 study) (175) with the most common duration being 2 months (5 studies).

Table 5.2 Characteristics of the ten studies of internal herbal medicine for psoriasis [adapted from Deng 2013 (135)]

First author, Publication year, Location, Duration, Follow-up	**Sample size (R/A), Gender (M/F), Age: mean ± SD (range), RCT design (T vs C)**	**Diagnosis, Outcome measures, Results**	**Dropouts, Adverse events (AEs)**	**Risk of Bias (SG, AC, BPt, BPl, BOA, IOD, SOR)**
Fan, M. 2005; Shandong, China; 60 days; 0.5-1 year	T:65/65, C:40/40; T:29/36, C:19/21; T: 30.5±9.1, (17-60) yrs, C: 32.1±10.9, (16-65) yrs; 2 gps, active-control: int HM + ext WM vs int APP + ext WM.	Psoriasis vulgaris; PASI: T≈C (t=1.25,p >0.05); Clearance rate: T≈C (χ^2=0.324,p >0.05); Response rate: T≈C (χ^2=0.375,p >0.05).	None; AEs (incidence, proportion): T: mild diarrhoea (2, 3.1%); C: total (37, 92.5%) including: dry mouth (22, 55.0%), cheilitis (3, 7.5%), dry skin (3, 7.5%), itching (3, 7.5%), increased serum lipids (4, 10.0%), headache (2, 5.0%). T<C (χ^2=84.81, p <0.01).	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Ho, S. G. Y. 2009; Hong Kong, China; 6 mths; NS	T:21/14, C1:20/19, C2:20/17; T:14/7, C1:18/2, C2:18/2; T:48.52, (25-80) yrs, C1: 38.45, (21-68) yrs, C2:43.45, (27-61) yrs; 3 gps, placebo & active-controls: int HM vs int APP vs int Plac.	Chronic plaque psoriasis; PASI: T>C1 (p=0.001), C1<C2 (p<0.01), T≈C2 (p>0.05); PGA: T>C1 (p=0.001), C1<C2 (p<0.01), T≈C2 (p>0.05); PDI: T≈C1≈C2.	T:7, C1:1, C2:3; AEs (incidence, issues): T: 48%, majority were infections & gastrointestinal issues, minority were developed abnormalities in liver function; C1: 65%, majority were nausea, vomiting & increased liver enzyme levels; C2: 30%, infections & increased liver enzymes.	SG: L AC: U BPt: H BPl: H BOA: L IOD: H SOR: L
Ma, W.L. 2010; Guangdong, China; 3 mths; NS	T:52/52, C:51/51; T:28/24, C:26/25; T: 39.04 ±18.58, (18-72) yrs, C: 40.67 ±13. 64, (18-74) yrs; 2 grs, active-control: int HM vs int APP.	Psoriasis vulgaris ('blood heat type'); Overall clinical efficacy: T≈C (p>0.05); PASI: T≈C (p>0.05).	None; AEs (T/C): cheilitis (0/25), headache (0/6), tinnitus (0/2), gastrointestinal disorder (5/0), abnormal liver function (0/4), dry skin & peeling (0/34), increased serum lipid (0/8). Incidence: T<C (p<0.05).	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Pandey, S.S. 1994; Varanasi, India; 12 wks; NS	T:34/30, C: 16/14; T:23/11, C:11/5; T:34.23 ±10.15, (18-59) yrs, C: 35.0 ±8.41, (22-54) yrs; 2 gps, double-blind, placebo-controlled: int HM + ext WM vs int Plac + ext WM.	Uncomplicated psoriasis vulgaris; PASI: T<C (p<0.001).	T:4, C:2; AEs: No toxic effects.	SG: U AC: L BPt: L BPl: L BOA: U IOD: U SOR: L

Qiu, S. 2005; Shanxi, China; 2 mths; NS	T:32/32, C:32/32, N:30/30; T:18/14, C:17/15,N:17/13; T: 30.42±8.57, (15-62) yrs, C: 33.34±8.21, (16-65) yrs, N: 31.45±7.5, (20-58) yrs; 3 gps, active-control with a normal reference group: int HM vs int APP vs non-intervention.	Psoriasis vulgaris in stable stage; Response: T≈C (p>0.05); Clearance: T<C (p<0.05); Lesion area, erythema, scaling, itching & PASI: reduced after study in T & C (p<0.01); Haemorheology parameters: reduced after study in T (p<0.05).	None; AEs: T: diarrhoea (2), constipation & vomiting (1); C: liver enzymes↑ (3), BUN (blood urea nitrogen) ↑ (1), serum lipid ↑ (5).	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Wu, Y.S. 2003; Shanghai, China; 8 wks; NS	T:30/30, C:20/20; T:24/6, C:15/5; T: 70.03±7.4 yrs, C: 67.10±4.5 yrs; 2 gps, active-control: int HM vs int APP.	Psoriasis vulgaris ('blood heat type'); PASI: T≈C (p=0.071); Clinical efficacy: T≈C (p>0.05); Syndrome score: T (post-care) > T (pre-care) (p<0.05); Pulse, urine & stool, and skin colour score: C (post-care) > C (pre-care) (p<0.05); Tongue score: C (post-care) ≈ C (pre-care) (p<0.05); Thirstiness score: C (post-care) < C (pre-care) (t=-6.84).	None; AEs: T: stomach disorder (n=2, 6.7%); C: obvious dry mouth, mild desquamation of lips (n=15, 75.0%).	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Xie, S.Q. 2009; Shanghai, China; 8 wks; NS	T:41/41, C:30/30; T:21/20, C:16/14; T:42.5, (16-69) yrs, C:37.5, (17-66) yrs; 2 gps, active-control: int HM vs int APP.	Psoriasis vulgaris; Clearance: T>C (p<0.05); Response: T≈C (p>0.05); PASI: T<C (p<0.05).	None; AEs: T<C (4.9% vs 80.0%, p<0.01). T: gastrointestinal disorder (2); C: dry skin & mucous (23), increased liver enzymes (2), increased serum lipids (2), headache, tinnitus, etc. (1), gastrointestinal disorder (2).	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Zhang, F.R. 1999; Shang Dong, China; 4 wks; NS	T:29/25, C:32/27; T:16/9, C:20/7; T:26.68±12.3, (16-45) yrs, C:28.62±14.23, (16-60) yrs; 2 gps, double-blind, placebo-controlled: int HM + ext WM vs int Plac + ext WM.	Psoriasis vulgaris; PASI: T<C (p<0.001); Clinical efficacy: T>C (p<0.001).	T:4, C:5; AEs: mild gastrointestinal tract (T=4) including 3 mild abdominal pain and 1 instance of diarrhoea; prolonged menstruation (T=1). C. no information on AEs reported.	SG: L AC: U BPt: L BPl: L BOA: U IOD: H SOR: L
Zhang, M. 2007;	T:NS/34, C:NS/33; T:25/9, C:27/6;	Moderate to severe plaque psoriasis; Reduction of PASI: T≈C (p>0.05);	NS; AEs: T: mild gastrointestinal tract (5), menstrual	SG: L AC: U

Sichuan, China; 8 wks; NS	T:32.4 (18-57) yrs, C:30.5 (21-52) yrs; 2 gps, active-control: int HM + ext WM vs int APP + ext WM.	PASI50/PASI70: T≈C (p>0.05); Change of DLQI: T≈C (p>0.05); DLQI ∝ PASI: C (r = 0.784, p <0.01), T (r = 0.851, p < 0.01); Change of DLQI ∝ Reduction of PASI: C (r = 0.625, p < 0.01), T (r = 0.578, p < 0.01).	disorder (1); C: dry mouth (26), dry skin/itching (17), cheilitis (12), palmoplantar desquamation & dry eyes (5), which were mild to moderate, and increased liver enzymes (1) & increased blood lipids (2).	BPt: L BPl: L BOA: U IOD: U SOR: L
Zhang, H.Y., 2008; Anhui, China; 3 mons; NS	T:34/34, C:18/18, N:10/10; T:17/17, C:10/8, N:5/5; T: 35.12 ±13.63 yrs, C: 34.50±12.99 yrs, N:27.40±8.68 yrs; 3 gps, activated-controlled RCT compared with normal population: int HM vs int APP vs non-intervention.	Progressive psoriasis vulgaris; Clinical efficacy: T≈C ($\chi 2$=0.416, p>0.05); PASI: T≈C (p>0.05); TNF-α & IL-8: significantly decreased in T gp (p<0.01).	No; AEs: NS.	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L

T: treatment group, C: control group, N: normal group, R/A: registration/analysis, M/F: male/female, NS: not stated, CM: Chinese medicine, WM: Western medicine, top.: topical, sys.: systemic, yrs: years, wks: weeks, mins: minutes, RCT: randomised clinical trial

Risk of Bias Categories

SG: Sequence Generation, AC: Allocation Concealment, BPt: Blinding of Participants, BPl: Blinding of Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SOR: Selective Outcome Reporting.

Risk of Bias Judgements

L: low risk, U: Unclear risk, H: High risk

Two studies compared internal HM with internal placebo and seven used a comparison with an internal APP (Table 5.3). Both comparisons were conducted in one study (175). Acitretin was the most common APP (176, 178-180, 182, 183). Other APPs included methotrexate (175) and vitamin A acid (174). PASI score was measured in each study. In addition to PASI, the outcome measures also included: clinical efficacy (174-183); Dermatology Life Quality Index (DLQI) (184), Physician's Global Assessment (PGA) and Psoriasis Disability Index (PDI) (175), Tumour necrosis factor alpha (TNF-α) and Interleukin 8 (IL-8) (182), CM syndrome score (179), and symptom scores (scaling, erythema, itching and lesion area) and haemorheology indices (178).

The internal HMs involved single herbs (n=2) and multiple ingredient formulae (n=8) (Table 5.3). The internal HMs were administered as: decoctions (n=6), capsules (n=3), or granule (n=1). Ten different herbs or formulae were investigated: aqueous extract of neem leaves in capsules, *Triptergium wilfordii* (TW) capsules, *Lanchuan Qingre* (also called *Longfuan*) decoction, *Wentonghuayu* formula in capsules, *Yinxiebing* formula as decoction, *Huoxue Sanyu Xiaoyin* decoction, *Qingre Jiedu* decoction, *Kangyin* No. 1 formula as decoction, *Haitang* decoction, and Compound *Zeqi* granule.

Three studies used 3 groups (175, 178, 182) and the remaining studies used 2 groups. In addition to the internal medicines, 3 studies used an external remedy as a co-intervention (174, 177, 183). In one study, internal methotrexate was combined with folic acid (175).

Table 5.3 Interventions used in the ten studies of internal herbal medicine for psoriasis [adapted from Deng 2013 (135)]

Study ID	Internal HM and ingredients	HM vs APP/Plac (T vs C)	Co-intervention (same in T&C)
Fan 2005	*Lanchuan Qingre* (Long fu an) decoction (250 ml): Ban lan gen (*Isatis tinctoria* root) 30g, Bai mao gen (*Imperata cylindrica* stem) 30g, Sheng di (*Rehmannia glutinosa* root) 30g, Zi cao (*Lithospermum erythrorhizon* root) 30g, Dan shen (*Salvia miltiorrhiza* root) 30g, Chi shao (*Paeonia veitchii* root) 10g, Chuan xiong (*Ligusticum wallichii* dried root) 10g, Tu fu ling (*Smilax glabra* root) 15g, Bai hua she she cao (*Oldenlandia diffusa* grass) 10g, Wu shao she (*Zaocys dhumnades*) 10g, Bai xian pi (*Dictamnus dasycarpus* bark) 10g, Gan cao (*Glycyrrhiza uralensis* root) 6g, etc, which was prepared by the authors' hospital (H062003001)	T: 250 ml daily divided into 2 administrations; C: vitamin A acid tablet (10 mg) manufactured by Shandong Liangfu Pharmaceutical Co., Ltd (H1097005). 20 mg daily divided into 2 administrations.	Skin heal Cream (Compound Triamcirolone acetonide Cream): 10g/tube, manufactured by Xinxiang Forever Pharmaceutical Co., Ltd. 2 X day.
Ho 2009	T: *Wen-tong-hua-yu* formula (capsule): Ma huang (*Ephedra sinica* herb) 6g, Chuan wu (*Aconitum carmichaeli* root) 10g, Baijiezi (*Brassica alba* seed) 10g, Rou gui (*Cinnamomum cassia* bark) 3g, Gan jiang (*Zingiber officinale* rhizome) 3g, Lu jiao shuang (*Cervus nippon* antler) 15g, Shu di (*Rehmannia glutinosa* root) 10g, Tu fu ling (*Smilax glabra* root) 60g, Bai xian pi (*Dictamnus dasycarpus* bark) 30g, Bai mao gen (*Imperata cylindrica* stem) 30g, Dan shen (*Salvia miltiorrhiza* root) 15g, Ji xue teng (*Spatholobus suberectus* stem) 30g, Zi cao (*Lithospermum erythrorhizon* root) 30g, Huai hua (*Sophora japonica* flower) 30g, Zhi gan cao (*Glycyrrhiza uralensis* root) 6g, Qing dai (*Indigo naturalis*) 6g.	T: NS; C1: Methotrexate, initial doses of 2.5–5 mg, increased to 10 mg/week if normality of complete blood count 1 week later, then added with 2.5 mg/week (≤30 mg/week) till a good clinical response. Folic acid: 5 mg daily; C2: identical placebo capsule used in T gp.	None.
Ma 2010	*Yinxiebing* formula: Tu bie chong	T: 1 decoction daily divided into two	None.

	(*Eupolyphaga sinensis*), Qing dai (*Indigo naturalis*), Gan cao (*Glycyrrhiza uralensis* root) each 10g, Dan shen (*Salvia miltiorrhiza* root), Bai hua she she cao (*Oldenlandia diffusa* herb), Sheng di huang (*Rehmannia glutinosa* root) each 30g. For dry stool, add Sheng da huang (*Rheum palmatum* root), Tao ren (*Prunus persica* seed), Huo ma ren (*Cannabis sativa* seed), Rou cong rong (*Cistanche salsa* herb), etc. For severe itching, add Quan xie (*Buthus martensii*), Wu gong (*Scoropendra subspinipes mutilans*), Wu shao she (*Zaocys dhumnades*), Chan tui (*Cyptotympana atrata* slough), Lu feng fang (*Polistes olivaceous* nest), etc. For head, face & upper limbs involved, add Jing jie (*Schizonepeta tenuifolia* herb), Fang feng (*Saposhnikovia divaricata* root), Bo he (*Mentha haplocalyx* leaf), Sang zhi (*Morus alba* branchlet), Gui zhi (*Cinnamomum cassia* twig), Ye ju hua (*Chrysanthemum indicum* flower), Ling xiao hua (*Campsis radicans* flower), etc. For trunk & lower limbs involved, add Yi ren (*Coix lacryma-jobi* seed), Shan yao (*Dioscorea opposita* root), Tu fu ling (*Smilax glabra* root), Bai zhu (*Atractylodes macrocephala* rhizome), Ba qia (*Smilax china* root), Gua lou gen (*Tirchosanthes kirilowii* fruit), Chuan niu xi (*Cyathula officinalis* root), etc. For whole body involved, add Wei ling xian (*Clematis* root).	doses (in the morning and in the evening); C: acitretin capsule (Fang xi) manufactured by Huapont Pharm Co., Ltd. 10 mg, 3 X day.	
Pandey 1994	Aqueous extract of neem leaves: Yin jian (*Azadirachta indica* leaf), major ingredient is Nimbidin.	T: 1 capsule, 3 X day, total 90 capsules; C: placebo- 1 capsule, 3 X day.	Ointment (5% crude coal tar & 3% salicylic acid in vaseline base): in night & next day to expose to sun for 15 mins after a thorough bath.
Qiu 2005	Huoxue Sanyu Xiaoyin decoction: San leng (*Sparganium stoloniferum* root) 10g, E zhu (*Curcuma phaeocaulis* rhizome) 10g, Tao	T: 1 decoction daily divided into two doses (in the morning and in the evening);	None.

	ren (*Prunus persica* seed) 10g, Hong hua (*Sophora japonica* flower) 10g, Ji xue teng (*Spatholobus suberectus* stem) 30g, Gui jian yu (*Euonymus alatus* herb) 30g, Bai hua she she cao (*Oldenlandia diffusa* herb) 30g, Dan shen (*Salvia miltiorrhiza* root) 30g, Chen pi (*Citrus tangerina* peel) 30g.	C: acitretin tablet manufactured by Chongqing Huapont Pharm. Co., LTD. 10 mg, 2 X day.	
Wu 2003	Qingre Jiedu decoction: Sheng di (*Rehmannia glutinosa* root) 30g, Chi shao (*Paeonia veitchii* root) 15g, Zi cao (*Lithospermum erythrorhizon* root) 30g, Ban lan gen (*Isatis tinctoria* root) 30g, Shan dou gen (*Sophora tonkinensis* root) 9g, Bai mao gen (*Imperata cylindrica* stem) 30g, Ba qia (*Smilax china* root) 30g, Ze qi (*Euphorbia helioscopia* herb) 15g.	T: daily, divided into 2 (in the morning & evening, after meal); C: acitretin (Neotigason), Roche, X20000166. 10 mg, 2 X day.	None.
Xie 2009	Kang Yin No. 1 formula: Sheng di huang (*Rehmannia glutinosa* root), Bai hua she she cao (*Oldenlandia diffusa* grass), Tu fu ling (*Smilax glabra* root) each 30g, Bai xian pi (*Dictamnus dasycarpus* bark) 20g, Dan shen (*Salvia miltiorrhiza* root), Da qing ye (*Isatis indigotica* leaf), Sheng huai hua (*Sophora japonica* flower), Ye jiao teng (*Polygonum multiflorum* dried vine) each 15g, Mu dan pi (*Paeonia suffruticosa* bark), Chi shao yao (*Paeonia veitchii* root), Zi cao (*Lithospermum erythrorhizon* root) each 12g, Shan dou gen (*Sophora tonkinensis* root), Gan cao (*Glycyrrhiza uralensis* root) each 6g.	T: 1 decoction daily divided into two administrations (after meals in the morning and in the evening); C: acitretin capsule manufactured by Huapont Pharm Co., Ltd. H20010788, 10 mg, 2 X day.	None
Zhang 1999	*Triptergium wilfordii* (TW) capsule: contained 3g TW crude drug (equivalent), which was extracted using alcohol & ethyl acetate at Dermatology Institute, Chinese Academy of Medical Sciences, and packed in identical opaque capsules.	T: 6 capsules daily; C: placebo capsule contained edible starch, packed in identical opaque capsule. 6 capsules daily.	Urea cream.
Zhang 2007	*Haitang* decoction: Kunming shan hai tang	T: 20-30 ml, 3 X day;	Pine Tar ointment: prepared by the

	(*Tripterygium hypoglaucum* root), Lai fu zi (*Raphanus sativus* seed), Fo shou (*Citrus medica* fruit), etc.	C: acitretin capsule, initial 20 mg, 1Xday for a week, then increased to 0.5-0.7 mg/(kg·d) (30-40 mg, 1 X day for 7 wks.	authors' hospital. 1 X day.
Zhang 2008	Compound Zeqi granule: Ze qi (*Euphorbia helioscopia* herb), Bai hua she she cao (*Oldenlandia diffusa* herb), Da qing ye (*Isatis indigotica* leaf), Ban lan gen (*Isatis tinctoria* root), Ji xue teng (*Spatholobus suberectus* stem), etc, which were provided by the authors' hospital.	T: 1 bag (30g crude drug), 3 X day for 3 mths; C: acitretin capsule (Fang xi) manufactured by Huapont Pharm Co., Ltd. 10 mg, 3 X day.	None.

T: treatment group, C: control group, HM: herbal medicine, SHM: systemic herbal medicine, SAPP: systemic anti-psoriatic pharmacotherapy, SPlac: systemic placebo

5.2.3.1 Description of studies

Compound *Zeqi* granule

Zhang *et al* (2008) compared Compound *Zeqi* granule with acitretin (*Fangxi*) in an active-controlled RCT with an untreated normal group as a reference (182). After 3 months, there were no significant differences in clinical efficacy and PASI score between the treatment group and the control group. Serum TNF-α and IL-8 were significantly decreased in both the test and control groups although the levels were still higher than in the normal group. The authors concluded that the formula could remarkably alleviate the symptoms of the disease and decreased the abnormal serum levels of TNF-α and IL-8.

***Azadirachta indica* leaf (capsule)**

Pandey *et al* (1994) reported a double-blind, placebo-controlled RCT of an aqueous extract of neem (*Azadirachta indica*) leaves in capsules with an ointment that contained 5% crude coal tar and 3% salicylic acid being used in both groups (177). After 12 weeks, there was a significant difference in PASI between groups in favour of the HM group. No side effects or toxicity issues were found during the trial. The authors concluded that the addition of *Azadirachta indica* produced a faster and better response compared to the conventional coal tar ointment alone.

***Triptergium wilfordii* capsule**

Zhang *et al* (1999) conducted a comparison between *Tripterygium wilfordii* (TW) capsule plus topical urea cream versus placebo plus urea cream in a randomised double blinded trial (181). After 4 weeks, there were significant differences in PASI score and clinical efficacy between groups in favour of TW. Regarding the treatment group, the authors concluded that TW exerted a remarkably quick efficacy in patients without any severe AEs in the short-term.

***Wentonghuayu* formula (capsule)**

Ho *et al* (2009) conducted a 3-group comparison of *Wentonghuayu* formula in the form of a capsule versus a placebo capsule versus methotrexate (MTX) for 6 months (175). The first two groups were double blind but the APP group was single blind owing to the difference in

the medication appearance compared to the HM and placebo capsules. PASI, Physician's Global Assessment (PGA) and Psoriasis Disability Index (PDI) were assessed on a monthly basis. The study confirmed the efficacy of methotrexate but found no difference between HM and placebo groups which were both less effective than the MTX group.

Qingre Jiedu decoction

Wu *et al* (2003) compared *Qingre Jiedu* decoction with acitretin (Neotigason) in elderly patients with 'blood-heat' type psoriasis vulgaris based on the principle of Chinese Medicine Syndrome Differentiation. They used PASI, clinical efficacy, and syndrome assessment (tongue, pulse, urine & stool, thirstiness level, and skin colour) as outcomes (179). After 8 weeks, no difference was found in PASI or clinical efficacy between the two groups. In terms of syndrome assessment, there were significant differences between pre-care and post-care in the treatment group. Whereas there was no significant difference in tongue, urine & stool, or skin colour between pre-care and post-care in the control group. The thirstiness level was aggravated in the control group during the study. Therefore, the authors considered that the HM formula produced effects comparable to acitretin in elderly patients with blood-heat type psoriasis vulgaris. In particular, the improvement in thirstiness was remarkably superior in the treatment group.

Lanchuan Qingre (aka *Longfuan*) decoction

Fan *et al* (2005) compared *Lanchuan Qingre* decoction with vitamin A acid tablets in patients with psoriasis vulgaris. All participants topically applied Skinheal Cream (compound triamcirolone acetonide cream) (174). After 60 days, there were no significant differences in PASI score, clearance rate or response rate between the two groups. Erythema and itching responded better to the herbal formula (decoction) whereas lesion size and thickness trended to improve in the vitamin A acid group. The AE incidence rates were 3.1% (treatment group) and 92.5% (control group), which were significantly different. The former was mild diarrhoea (n=2), and the latter involved: dry mouth (n=22), cheilitis (n=3), dry skin (n=3), itching (n=3), increased serum lipids (n=4) and headache (n=2). The authors concluded that *Lanchuan Qingre* decoction was an effective formula for psoriasis with fewer AEs than vitamin A acid tablets.

Huoxue Sanyu Xiaoyin decoction

Qiu *et al* (2005) assessed the efficacy of *Huoxue Sanyu Xiaoyin* Decoction on psoriasis vulgaris in a 3-group RCT controlled by acitretin, with a normal population as the reference for haemorheology parameters (178). After 2 months, there was no significant difference in response rate between groups but there was a significant difference in clearance rate (T 46.88% vs C: 56.25%). In terms of lesion area, erythema, scaling, itching & PASI score, reductions were found in both groups during the study. In the treatment group, haemorheology parameters reduced during the treatment period in the HM but remained higher than in the normal group. The authors concluded that *Huoxue Sanyu Xiaoyin* decoction showed remarkable effectiveness in psoriasis and its mechanism of action possibly involved the promotion of microcirculation.

Haitang decoction

In Zhang *et al* (2007), the comparison was between the retinoid acitretin and the HM *Hai Tang* decoction with topical pine tar ointment being used in both groups but the authors placed the HM in the control group and the report focused on the result for acitretin (183). The scores for PASI and DLQI indicated improvements in both groups but there was no statistic reported for the between-group differences in the paper. The authors concluded that acitretin was effective in moderate to severe plaque psoriasis and was comparable to *Haitang* decoction.

Kangyin No. 1 formula (decoction)

Xie *et al* (2009) conducted a clinical comparison between *Kangyin* (No.1) formula decoction and acitretin capsules (180). After 8 weeks, significant differences were found in clearance rate and PASI score between the two groups, but there was no significant difference for response rate. The incidence of adverse effects in the treatment group was lower than in the control group. Therefore, the authors thought the HM was a safe and effective medication with an efficacy similar to that of acitretin but with fewer side effects.

Yinxiebing formula (decoction)

Ma *et al* (2010) compared *Yinxiebing* Formula with modifications according to symptoms with acitretin in patients diagnosed with ‘blood heat type’ psoriasis vulgaris according to

Chinese medicine principles (176). For clinical efficacy and PASI score, there were no significant differences between the two groups after 3-months of treatment. Meta-analysis was applied to the clinical efficacy scores but the PASI score data were not suitable for analysis. The authors concluded that *Yinxiebing* formula can be used as a routine treatment for blood-heat type psoriasis and had an efficacy comparable to that of acitretin.

5.2.3.2 Methodological assessment

Methodological assessment was undertaken according to the Cochrane Handbook, the relevant Risk of Bias evaluations (171) are summarised in Table 5.2. All studies stated 'randomized' or used a similar expression. Three stated the specific method of random sequence generation: including 'shuffling random cards' (175), and 'random number table' (181, 183), which were judged as low risk on this item. As one study used sequentially numbered drug containers, it was judged as low risk on the method of allocation concealment (177). In two placebo-controlled studies, identical capsules were used to blind the participants, so these studies were assessed as low risk of bias on this item (177, 181). In a 3-group study that compared a placebo group and APP group to the HM group (175), the APP was presented in a different form to the placebo and HM, so the study was judged as high risk on blinding of participants. The remaining 7 studies were also assessed as high risk for this item.

The above eight studies were also judged as high risk of bias for blinding of personnel whereas the remaining two were considered low risk (177, 181). One study was blinded to outcome assessors and assessed as low risk (175). The others did not provide any information on this item so they were judged as unclear risk of bias. As missing outcome data due to dropouts resulted in imbalance in numbers across the intervention and control groups, two studies were judged as high risk of bias on incomplete outcome data (175, 181). Another two studies were judged as unclear risk of bias for missing data since they either did not provide reasons for dropouts (177), or the enrolment numbers of participants were not stated (183). The other studies reported all patients completed the study and were judged as low risk. Each study reported all outcomes stated in the methods, so bias regarding selective reporting was judged as low. There were too few studies (less than 10) in each of the two groups for assessments of publication bias.

5.2.3.3 *Meta-analysis*

Meta-analyses were conducted for PASI and clinical efficacy,in RevMan 5.1 (Table 5.4). All studies provided PASI data but the PASI values in one study were significantly different between groups at baseline and therefore not suitable for the pooling of between groups effects at the end of treatment, so the pre- and post- intervention scores were assessed for this study (176). Two studies did not provide suitable data on clinical efficacy (177, 182). Therefore, RevMan 5.1 was applicable to 10 studies for PASI (174-183) and 8 studies for clinical efficacy (174-176, 178-181, 183).

The other outcome measures were varied and were each used in only one study so these were not included in the meta-analyses.

Table 5.4 Distribution of data available for meta-analysis in Review Manager 5.1 by outcome measure and study design

Study design / **Outcome measures**	**Int. HM** **vs** **Int. Placebo***	**Int. HM** **vs** **Int. APP***
Clinical efficacy	Ho 2009 Zhang 1999	Fan 2005 Ho 2009 Ma 2010 Qiu 2005 Wu 2003 Xie 2009 Zhang 2007
Scaling score	X	Qiu 2005
Erythema score	X	Qiu 2005
Itching score	X	Qiu 2005
Lesion area	X	Qiu 2005
Haemorheology	X	Qiu 2005
CM syndrome score	X	Wu 2003
TNF-α	X	Zhang 2008
IL-8	X	Zhang 2008
PASI	Ho 2009	Fan 2005

	Pandey 1994 Zhang 1999	Ho 2009 Ma 2010[#] Qiu 2005 Xie 2009 Wu 2003 Zhang 2007 Zhang 2008
DLQI	X	Zhang 2007
PGA	Ho 2009	Ho 2009
PDI	Ho 2009	Ho 2009

*: including co-intervention used in both arms

#: PASI baseline differences between treatment group and control group. This study was not suitable for meta-analysis - so pre- and post- intervention analyses were conducted.

HM: Herbal Medicine, APP: Anti-psoriatic Pharmacotherapy, CM: Chinese Medicine, WM: Western Medicine, Int. internal treatment, Ent.: external treatment, PASI: Psoriasis Area Severity Index, DLQI: Dermatology Life Quality Index, PGA: Physician's Global Assessment, PDI: Psoriasis Disability Index

***Meta-analysis* of PASI score**

For PASI score, nine studies provided data suitable for meta-analysis. These were divided into two groups based on study design: 1. Internal HM versus Internal Placebo, and 2. Internal HM versus Internal APP. These included studies with identical co-interventions used in both arms (Table 5.4). Since PASI baseline in the HM group was significantly higher than in the acitretin group at the beginning of Ma *et al* 2010, this study was not included in the pool. At end of treatment, PASI reduced in both groups and there was no difference between the two groups (176).

Both the Internal HM versus Internal Placebo (175, 177, 181), and Internal HM versus Internal APP (174, 175, 178-180, 182, 183) groups included studies that had identical co-interventions used in both arms (Table 5.4).

Group 1. Internal HM vs Internal Placebo (3 studies, 6 groups)

For Pandey *et al* 1994 and Zhang *et al* 1999, which both used single HMs in capsules, i.e. aqueous extract of neem leaves (*Azadirachta indica* leaf) and *Tripterygium wilfordii* (TW) respectively, the HMs were both superior to the placebo capsules, (MD -4.73; 95% CI: -6.49, -2.97, and MD -7.52; 95% CI: -8.45, -6.59 respectively). However, no significant difference was found between *Wentonghuayu* formula (capsule) and its placebo capsule (MD 2.10; 95% CI: -4.93, 9.13) in Ho *et al* 2009. These meta-analysis results supported the authors' conclusions (Fig. 5.2).

The pooled data found internal HM was superior to internal placebo for PASI score (MD -5.00; 95% CI: -8.20, -1.81) but the heterogeneity was high (85%). When Zhang *et al* (1999) was removed the heterogeneity was reduced (71%) but remained high. This, heterogeneity could have resulted from the following differences between the studies: treatment duration (1, 3, or 6 months), intervention (multi-herb formula vs single herb). Another reason could be the severity of the psoriasis. In Zhang *et al*. 1999 the mean score at baseline was about 10, but the mean PASI score was about 19 in Pandey 1994 and it was 18 to 22 in Ho *et al*. 2009.

Group 2. Internal HM versus Internal APP (7 studies, 14 groups)

For the comparison with acitretin and various HM preparations, there were no significant differences in PASI score as follows: *Huoxue Sanyu Xiaoyin* Decoction (MD -0.05; 95% CI: -0.46, 0.36) (178), *Qinre Jiedu* decoction (MD 0.83; 95% CI: -1.35, 3.01) (179), *Kangyin* No.1 formula (MD -0.78; 95% CI: -1.64, 0.08) (180), *Hai Tang* decoction (MD -1.05; 95% CI: -2.41, 0.31) (183), and Compound *Zeqi* granule (MD -1.17; 95% CI: -3.09, 0.75) (182). These results were consistent with the authors' conclusions.

The pooled data showed no difference between the HMs and acitretin (MD -0.39; 95% CI: -0.92 to 0.15, I^2=27%) on PASI score. *Lanchuan Qingre* decoction appeared superior to vitamin A acid on PASI score (MD -0.45; 95% CI: -0.76, -0.14) (174) whereas the authors reported no significant difference between the two groups. Methotrexate was superior to *Wentonghuayu* formula in Ho *et al* 2009 (MD 10.30; 95% CI: 3.90, 16.70). This result supported the authors' conclusions.

For the pooled data of Group 2, no significant difference between internal HM versus internal APP was found on PASI score (MD -0.36, 95% CI: -0.93, 0.20, I^2=64%) (Fig. 5.2). The high heterogeneity was related to Ho *et al* 2009. When this study was removed the pooled result still showed no difference but with low heterogeneity (MD -0.37, 95% CI:-0.68, -0.07, I^2=19%).

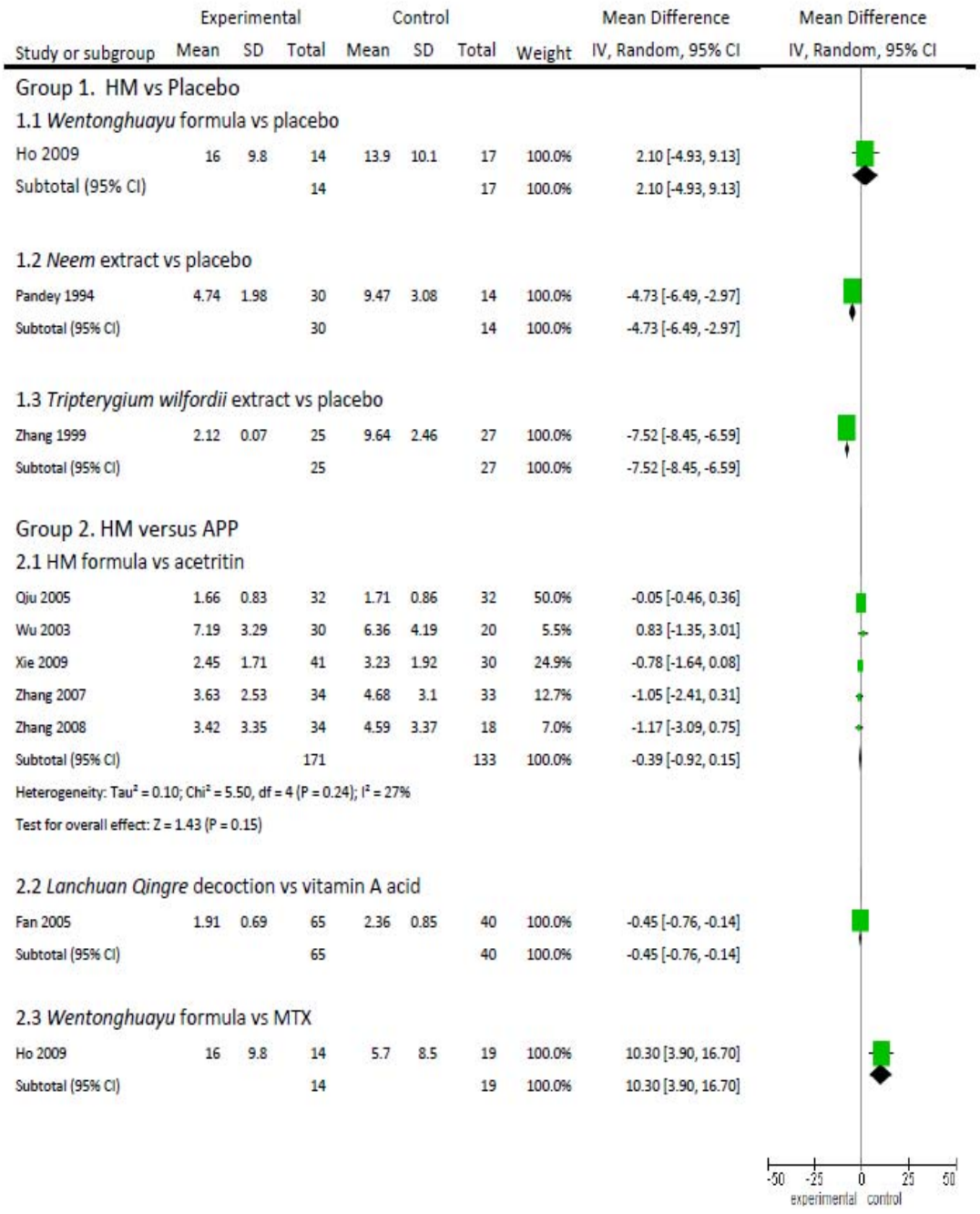


Fig. 5.2 Forest plot of PASI score: Internal Herbal Medicine (HM) versus placebo or Anti-psoriatic Pharmacotherapy (APP) (with or without co-intervention used in both groups)

Meta-analysis **of Clinical efficacy**

For clinical efficacy, the rates were generated by calculating PASI scores based on a number of different thresholds according to the particular study. For data pooling, to enable comparison between studies only cases having at least a 50% efficacy rate or a 50%

reduction in PASI were included (185). Results were analysed with risk ratio (RR) and a random-effects model was used as the calculation methods for clinical efficacy were different between studies. In the meta-analyses, a higher score showed greater efficacy.

For the eight studies that provided data suitable for meta-analysis, 2 groups were identified as follows: 1. Internal HM versus Internal Placebo (175, 181), and 2. Internal HM versus Internal APP (174-176, 178-180, 183). These included studies that used identical co-interventions in both arms (Table 5.4).

Group 1. Internal HM vs Internal Placebo (2 studies, 4 groups)

For Ho *et al* (175), no significant difference between *Wentonghuayu* formula (capsule) and placebo (capsule) was found on clinical efficacy (RR 0.61, 95% CI: 0.13, 2.84). However, the comparison between *Tripterygium wilfordii* (TW) capsule and placebo, with urea cream as co-intervention, showed a significant difference (RR 8.64, 95% CI: 2.96,25.19) in favour of TW (181). Both meta-analysis results were consistent with their respective authors' conclusion.

For the pooled data, no significant difference was found between HM and placebo on clinical efficacy (RR 2.43, 95% CI: 0.18, 32.75) but the heterogeneity was high (87%) (Fig.5.3). This could be due to the following differences between the studies: treatment duration (6 months vs 1 month) and intervention (multi-herb formulation vs single herb). The high heterogeneity indicated that the pooled effect was not interpretable.

Group 2. Internal HM versus Internal APP (7 studies, 14 groups)

No significant difference was found between acitretin and its five different HM comparators: *Yinxiebing* formula (RR 1.00; 95% CI: 0.96, 1.04) (176), *Huoxue Sanyu Xiaoyin* decoction (RR 0.86; 95% CI: 0.67, 1.09) (178), *Qinre Jiedu* decoction (RR 0.67; 95% CI: 0.32, 1.38) (179), *Kangyin* No.1 formula (RR 1.10; 95% CI: 0.84, 1.43) (180), and *Hai Tang* decoction (RR 1.11; 95% CI: 0.79, 1.55) (183).

The pooled data showed no difference between the HMs and acitretin (RR 1.00; 95% CI: 0.96, 1.04, I^2 = 0%) on clinical efficacy. For Vitamin A Acid, there was no significant difference in comparison with *Lanchuan Qingre* decoction in Fan *et al* 2005 (RR 0.95; 95% CI: 0.81, 1.11). However, for Ho *et al* (2009), methotrexate was superior to *Wentonghuayu*

formula (RR 0.18; 95% CI: 0.05, 0.67). These results were consistent with the authors' conclusions (Fig. 5.3).

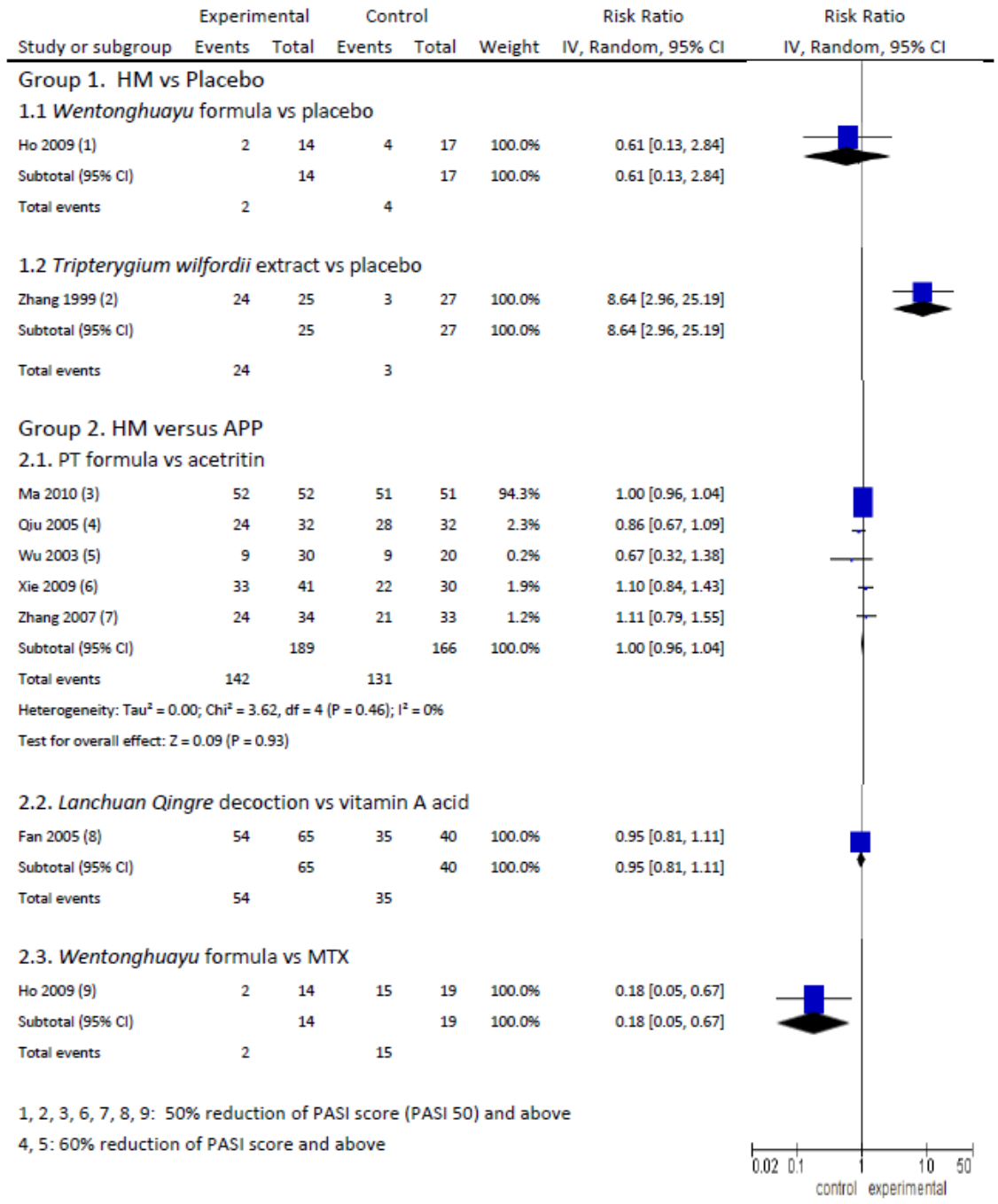


Fig. 5.3 Forest plot of clinical efficacy: Internal Herbal Medicine (HM) versus placebo or Anti-psoriatic Pharmacotherapy (APP) (with or without co-intervention used in both groups)

5.2.3.4 Adverse events (AEs)

Zhang *et al* 2008 did not provide any information on adverse events (182), Zhang *et al* 2009 only reported AEs for the treatment group (181) and Pandey *et al* 1994 reported there were 'no toxic effects' (177). The most frequent side effects were xerosis including cheilitis, dry mouth and dry skin, and gastrointestinal reactions such as vomiting and diarrhoea. Other AEs included elevated blood lipids, elevated liver enzymes, elevated blood urea nitrogen (BUN) and reduced white blood cells (WBC). 26 AE cases were reported among the 257 participants in the assessable treatment groups (10.12% incidence rate) whereas 89 AEs in 109 participants were reported in the APP control groups, so there was a higher incidence rate (81.65%) in the four accessible APP control groups. In the three placebo groups, 6 AEs were reported among the 58 participants (10.34% incidence rate).

The AEs incidence was pooled for 7 studies. For internal HM versus internal placebo (175, 177, 181), no difference was found (RR 2.80, 95% CI: 0.73, 10.74, I^2=28%) (Fig. 5.4). For internal HM versus internal APP (174, 175, 179, 180), there was a lower AE incidence in the HM groups (RR 0.12, 95% CI: 0.02-0.89, I^2=93%). The high heterogeneity was due to Ho *et al*. 2009. When it was removed, the heterogeneity reduced to zero.

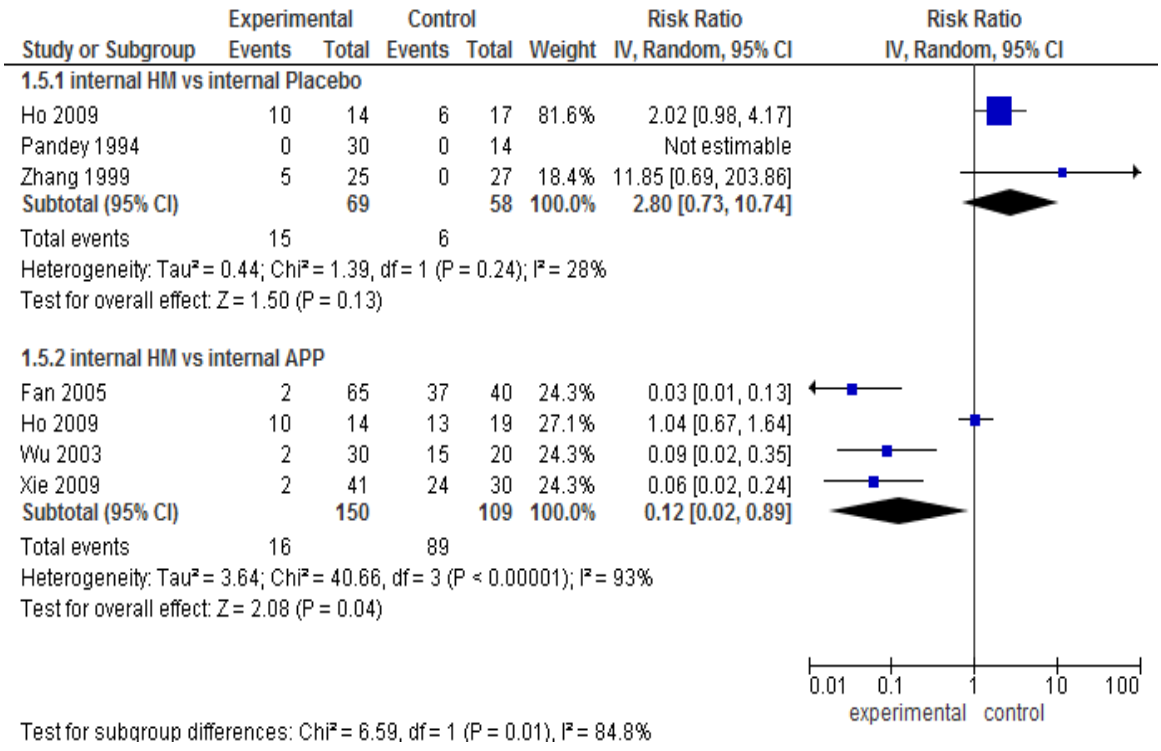


Fig. 5.4 Forest plot of Adverse Events (AEs): Internal herbal medicine (HM) versus internal placebo or Anti-psoriatic Pharmacotherapy (APP) (with or without co-intervention used in both groups)

The incidence of abnormal laboratory test results was zero in the HM groups with respect to: elevated blood lipids (vs 11.29 % for APP groups), elevated liver enzymes (vs 6.02 % for APP groups), elevated BUN (vs 3.13 % for APP groups), or reduced WBC (vs 0 % for APP groups). None of the above abnormal laboratory test results were associated with hospitalisation. In one study, AEs led to short-term cessation of vitamin A acid treatment but this was resumed after the AEs had subsided (see Fan 2005). In Zhang *et al* 1999, 2 dropouts in the HM group resulted from gastrointestinal reactions. In other cases the AEs did not lead to discontinuation of participation.

5.2.3.5 Principal herbs used in the studies

Among the examined test HMs, 39 different medicinal plants were internally applied in two single herb preparations and nine multiple-ingredient formulae that were administered as granule (n=1), capsule (n=3), or decoction (n=6). The most commonly used individual herbs in the internal management of psoriasis were the three herbs that were each used in 5 studies: *Di huang* (*Rehmannia glutinosa* Libosch, root) including *Sheng di* (dried root) and *Shu di* (steamed root), *Dan shen* (*Salvia miltiorrhiza* Bge., dried root) and *Bai hua she she cao* (*Oldenlandia diffusa* (Willd.) Roxb., herb). These were followed by two herbs that were used in 4 studies each: *Zi cao* (*Lithospermum erythrorhizon* Sieb.et Zucc., root) and *Gan cao* (*Glycyrrhiza uralensis* Fisch., dried root). Six herbs each appeared in 3 studies: *Bai mao gen* (*Imperata cylindrica* (L.) P.Beauv. var. major (Nees) C.E.Hubb, stem), *Ban lan gen* (*Isatis tinctoria* L., root), *Bai xian pi* (*Dictamnus dasycarpus* Turcz., bark), *Chi shao* (*Paeonia veitchii* Lynch, root), *Ji xue teng* (*Spatholobus suberectus* Dunn., stem), and *Tu fu ling* (*Smilax glabra* Roxb., root). Five herbs were used twice and 23 were applied once.

5.2.4 Discussion

All studies were found to demonstrate at least some methodological reporting issues. Only three studies stated the method of sequence generation and one reported allocation concealment. Two were blind to participants and one also was blind to outcome assessment. In six studies, outcome data were provided completely. In general, the better quality trials appeared to be Pandey *et al* 1994, Zhang *et al* 1999 and Ho *et al* 2009.

Local xerosis (lips, mouth and skin) and gastrointestinal reactions were mostly frequently reported AEs in these trials of internal HM for the management of psoriasis. Regarding AE incidence, it was significantly lower in the internal HM groups than in the internal APP groups (10.12% vs 81.65%). Also the AE incidence in the HM groups was similar to the internal placebo groups (10.12% vs 10.34%). For the laboratory test results including: elevated Blood Lipids, elevated Liver Enzymes, elevated BUN, and reduced WBC, there were no adverse findings for the HM groups. Therefore, the internal herbal medicines for which safety data were reported appeared to be safe for psoriasis management at the dosages and in the timeframes used. However there was considerable variation in the adequacy of AE reporting with no reporting in Zhang HY 2008 and brief reporting in Pandey 1994. Also the following three HMs, *Dictamnus dasycarpus*, *Tripterygium wilfordii* and Neem (*Azadirachta indica*), have been associated with safety concerns in the literature.

Dictamnus dasycarpus (Bai xian pi) was included in the formulations used in three studies (174, 180, 186). AEs involving acute hepatitis have been reported which appear to have been due to the oral use of this herb (187-190). In Xie *et al* 2009, two AEs in the acitretin group were reported that related to increases in liver enzymes but none were reported in the HM group (180). In Ho *et al* 2009, liver enzyme abnormalities were reported in all three groups including the placebo group but the exact incidence of increased enzymes in each group cannot be determined from the report. Some dropouts resulted from acute hepatitis but no information was provided on the number, group or causes of the hepatitis (186). In Fan *et al* 2005, liver enzymes were not assessed but two AEs involving mild diarrhoea in the HM group were reported but there were no dropouts (174). Whether the addition of *D. dasycarpus* to the HM formulations in these studies had adverse effects on liver function is not possible to determine from the reported data. Some experimental evidence has also suggested that *D. dasycarpus* had anti-inflammatory effects (157), however we urge caution and careful monitoring if this plant is used in therapy or in clinical trials.

T. wilfordii (Lei gong teng) was used in one of the included studies (181). Experimental studies of *T. wilfordii* have shown it to have immunosuppressive activity but it is considered a toxic plant and crude preparations of this plant have been associated with a wide range of AEs including renal failure, subacute hepatic necrosis and chromosomal aberrations (191, 192). Consequently, such crude preparations are no longer used and a number of extracts have been developed that show reduced toxicity, including ethyl acetate and chloroform–

methanol extracts of the herb (191). Although there were no serious AEs reported for the ethyl acetate extract used in the included study (181), and the results of the blood, neurological, liver function and kidney function tests were normal in this study, there were some instances of AEs typically associated with this plant and other studies have reported serious AEs, so the safety profile of *T. wilfordii* and its extracts remains a concern. Consequently, this plant should not be used in the clinical management of psoriasis (192).

Various preparations of *Azadirachta indica* have received research attention for their anti-inflammatory (193), cancer-preventative (194), anti-proliferative (195-197), contraceptive, and anti-parasitic effects (198). However, Neem preparations have raised safety concerns including dermatological reactions related to Neem oil (199). *Azadirachtin*, a Neem constituent, has shown *in-vitro* genotoxic effects (200) but another *in-vivo* experiment found no cumulative effects on postnatal development in rats (201). Other studies have reported that a methanolic extract of Neem leaves may affect fertility in female rats (202), Neem oil adversely affected organ function in mice (203) and an ethanolic stem bark extract induced a similar effect in rats (204).

In a review of Neem safety, Boeke *et al* 2004 demonstrated that the non-aqueous extracts were more toxic than the aqueous extracts but the safe dose in humans was difficult to quantify with the best estimate being 0.3 mg/kg bw/day (205). Pandey *et al* 1994 found that when an aqueous extract of Neem leaf was used there was no evidence of toxicity during the study but the dosage was not clearly specified (177). In another human study, an acetone-water Neem leaf extract (1.0 g/day) was found to have no toxicity in HIV/AIDS after 12 weeks (206). Since there is a variety of Neem preparations (including seed oils, stem bark, root bark, leaf & flower) in use as topical and systemic medicines and in pesticides and there are a variety of extraction processes used, it is hard to make an overall evaluation of the safety of Neem use in psoriasis, therefore caution is urged.

In terms of the efficacy of the HMs, the meta-analyses of the outcomes for clinical efficacy based on PASI 50 and PASI score, found no differences between the internal HMs and acetritin based on five studies and there was no difference between HM and vitamin A acid based on one study. Therefore, the internal HMs appear to have exerted effects similar to those of acitretin and vitamin A acid. One study showed an internal HM to be inferior to MTX.

For the comparisons of internal HM versus internal placebo, the data showed a significant improvement for PASI score for Neem leaf extract and *T. wilfordii* extract (177, 181), and there was improved clinical efficacy for *T. wilfordii* extract.

In contrast, the study by Ho *et al* 2009 found no effect for the HM on PASI or clinical efficacy (186). It is notable that the HM used in Ho *et al* 2009 was a commercial formulation that is not similar to the HM formulations used in the other studies and is not typically recommended for psoriasis (106). The method used in this study also suffered from a lack of blinding. The magnitude of effect in the placebo group was large with 21.4% of participants achieving PASI 50 and 18% achieving PASI 75 which is at the top of the range reported for control groups by Lamel *et al* 2012 and well above the average of 4.1% (207).

As a primary endpoint, PASI is considered as a detailed and validated measure of psoriasis severity (170). Although PASI 75 is frequently used a major endpoint in clinical trials, PASI 50 also provides a clinically meaningful measure of improvement in psoriasis (173). Therefore, the improvements in clinical efficacy based on PASI 50 or above reported in the trials represent potentially clinically important results that require further consideration.

In total, nine studies reported that HM was either superior to placebo or had effects that were not significantly different to those of the APPs acitretin and vitamin A acid. Of these studies, two used single herb extracts while the remaining seven used multi-ingredient formulae. Amongst these formulae, the most frequently used individual HM was *Bai hua she she cao* (*Oldenlandia diffusa* herb) which was used in five studies. This was followed by *Dan shen* (*Salvia miltiorrhiza* dried root) (n=4), *Sheng di* (*Rehmannia glutinosa* dried root) (n=4), then *Zi cao* (*Lithospermum erythrorhizon* root) (n=3), *Chi shao* (*Paeonia veitchii* root) (n=3) and *Gan cao* (*Glycyrrhiza uralensis* root) (n=3). To further explore the possible effects of the individual HMs used in multiple studies, evidence derived from experimental studies of the actions of *O. diffusa*, *R. glutinosa*, and *S. miltiorrhiza* that are relevant to psoriasis were evaluated. This aspect is discussed in chapter 7.

5.2.5 Limitations of this review

A major limitation of this review is that the methodological issues identified in the clinical trials increase the risk of bias in the reported results. Lack of blinding or ineffective blinding of the participants and the personnel in seven of the ten trials could have influenced the

assessment of PASI scores and the reporting of adverse events. In terms of the magnitude of the effects of the interventions, assessments were only available for PASI 50 and above, not for PASI 75, so comparisons between HM and APP were based on which is considered the minimum threshold for clinical efficacy. Nevertheless, as the study by Carlin *et al* (2004) found, PASI 50 is still an important endpoint for the assessment of a clinical intervention (173).

The small sample sizes and relatively short durations of the included trials also limit the meaningfulness of the results. Moreover, the lack of duplication of studies that use the same intervention limits the reliability of results.

The statistical heterogeneity for pooled studies of HMs versus acetritin was low, but the variability in the test interventions, the methods used and the way outcomes were measured could all have affected the meta-analysis results. Nevertheless, there is similarity between a number of the HM interventions in terms of the main plants used. Also, there are experimental studies that suggest that these plants are not inactive and at least some of their pharmaceutical actions are of relevance to psoriasis (see chapter 7 for more detail). It is also possible that additive and/or synergistic effects in the multi-ingredient HMs may have increased efficacy beyond that expected of a single plant extract (208).

Despite these cautions on the over-interpretation of the evidence from the clinical studies, the analysis of such studies can help to identify directions for further and more rigorous clinical and experimental research endeavours.

5.2.6 Summary

This systematic review and meta-analysis of ten clinical trials on herbal medicines used internally for psoriasis found that there were short-term responses that were greater than placebo in two out of three studies. When compared to APPs, responses were not inferior to acetritin in seven studies, similar to vitamin A acid in one study and inferior to MTX in one study. These responses were based on PASI 50 or greater so they appear to be clinically significant.

While these potential benefits for clinical response were similar to those of the conventional APP interventions, the AE incidence significantly was lower in the HM groups and the HM

used in the trials appear to have been safe, at least in the short term. However, AE reporting may have been inadequate in some trials and three of the herbs have raised safety concerns. Also, methodological weaknesses in the trials limit the meaningfulness of the results, so well-designed trials are needed to further evaluate the potential benefits identified in this review.

Chapter 6: Results of systematic review of RCTs on external HM for psoriasis

As stated in Chapter 5, eligibility of the studies to be included in our meta-analysis was established using our standard procedure. The studies included in analysis can be divided into 3 categories: 1. comparisons of topical treatments using a single-herb preparation with placebo or anti-psoriatic pharmacotherapy (APP); 2. comparison of the effect of topically applied herbal formula and that of placebo or APP and 3. comparisons of treatment with HM in combination with APP and with APP alone. Categories 1 and 2 also include studies in which the primary comparison is between externally administered HM and external placebo or APP but with an additional intervention (the same in both groups) such as another pharmaceutical or an internal HM treatment. The data in the following three reviews has been published (157-159).

6.1 Results of systematic review 2: Single herbs for the external management of psoriasis: A systematic review with meta-analysis of RCTs

6.1.1 Introduction

At present, almost half of the people with skin disorders in North America and Europe receive complementary and alternative medicine (CAM) treatment. CAM that includes herb-based preparations is often combined with conventional pharmacotherapy (54, 160-162). Therefore, practitioners and dermatologists should be aware of the properties of single herbs and their extracts commonly used in psoriasis therapy. This review analyses the available evidence regarding the efficacy and safety of single-herb preparations used for the external treatment of psoriasis.

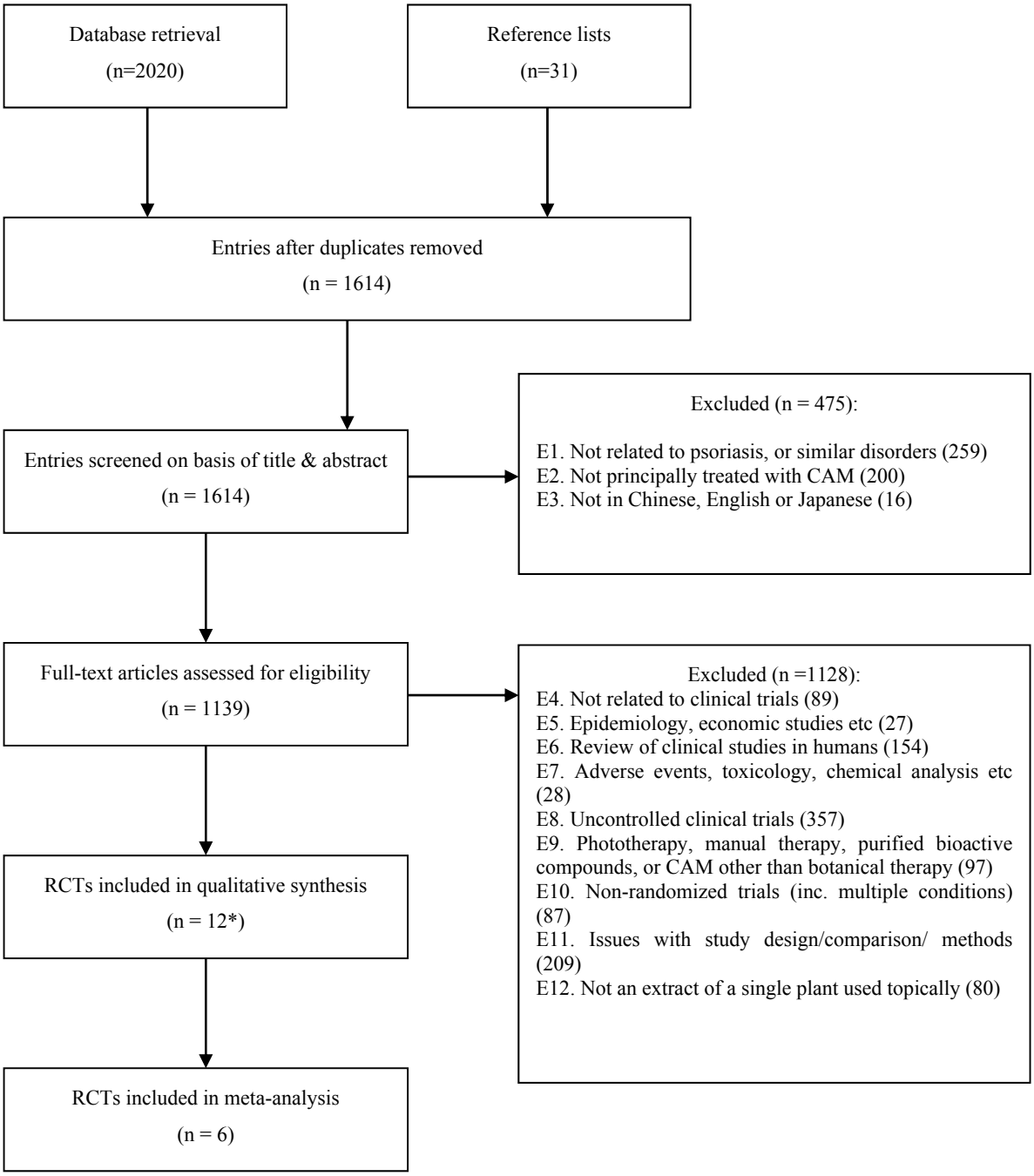
6.1.2 Method

We evaluated several reviews describing the effects of externally applied HM in the management of psoriasis (35, 36, 48, 157, 164). To find the relevant publications, we searched the following databases: EMBASE, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI) Database and Chinese Scientific Journals Full Text Database (CQVIP) (up to September 2012). Search terms comprised 3 groups: clinical

condition; intervention and study type, with adjustments for different databases (see Chapter 4 for lists of terms). We also searched reference lists in review articles.

Herb extracts were simply defined as preparations of plant origin. We excluded purified bioactive components, vitamins and homeopathic preparations. Languages were limited to English, Chinese or Japanese. In comparisons between RCTs analysed in this subsection, only studies on topical applications of single herbs were included. Herbal formulae and interventions that combined HMs with pharmaceuticals were not included. Other substances used in the vehicle preparation, necessary for the extraction or used as preservatives were allowed. The included studies compared the effect of topical treatment with a single-extract preparation with that of placebo vehicle base, other topical placebo, no treatment or conventional topical pharmacotherapy.

Two of the researchers, SD and BHM, conducted the searches and extracted the characteristics of each study. The collected information included the location, duration, design, participants, interventions, outcome measures, dropouts, adverse events and assessed risk of bias (171). The third researcher, ALZ, participated in the discussions and helped to resolve any disagreements if agreement could not be reached. A flowchart for the process of study selection is presented in Fig. 6.1. Review Manager 5.1 was employed for data analysis. Risk ratio (RR) with a 95% confidence interval (95% CI) or mean difference (MD) was used with fixed- or random-effect models, depending on heterogeneity (172).



* 2 RCTs derived from 1 article

Fig. 6.1 Flow chart of selection of randomised controlled trials (RCTs) on externally applied single-herb preparations used for treating psoriasis [adapted from Deng 2013 (159)]

6.1.3 Results

In total, 2,020 potential entries were obtained from the database searches and 31 studies were identified from reference lists. After the removal of duplicates, the remaining 1,614 records were screened and the full text of 1,139 entries was obtained. Among these, 11 articles satisfied the inclusion criteria, resulting in 12 RCTs (209-219).

The 12 RCTs were from the following countries: China (3), Germany (2), USA (2), USA and Canada (1), Canada (1), Thailand (1), Denmark (1) and Pakistan (1). Most papers were written in English (11), and 1 paper was in Chinese. Half-body intra-patient bilateral comparisons were reported in 7 of these studies (209, 213-216, 219). The 12 RCTs had initially enrolled 858 patients, 790 of whom (aged 16–85 years) participated in the studies (Table 6.1). The greatest sample size was 184 participants (218). All the participants were diagnosed with mild to moderate psoriasis. In 11 studies, all criteria for inclusion and/or exclusion were specified. The intervention courses lasted from 4 weeks (5 studies) to 6 months (1 study). A topical single-herb preparation and topical placebo were used in 9 RCTs, and topical APPs, including dithranol (209), calcipotriol plus fluticasone propionate (213) and triamcinolone acetonide (212), were used in 3 RCTs. Outcome measures included clinical efficacy (n = 8) (212-219), symptom score (n = 6) (211-215, 217), Psoriasis Area and Severity Index (PASI) (n = 7) (210-213, 215-217), Dermatology Life Quality Index (DLQI) (n = 2) (212, 213) and Quality of Life Index (QLI) (n = 1) (210).

Table 6.1 Characteristics of the 12 studies on topical preparations of single herbs for treating psoriasis [adapted from Deng 2013 (159)]

First author, Publication year, Location, Duration, Follow-up	**Sample size (R/A), Gender (M/F), Age: Mean ± SD (Range); RCT design (T vs C)**	**Preparation ingredients, Application, Manufacture**	**Diagnosis, Outcome measures, Results**	**Dropouts (reasons), Adverse events (AEs)**	**Risk of Bias (SG, AC, BPt, BPl, BOS, IOD, SOR)**
Augustin, M. 1999; Freiburg, Germany; 4 weeks; NS	60/49; NS; NS; half-body, 1 group, active- control.	T: *Mahonia aqulifolium* ointment, 3 X day, NS. C: dithranol in rising concentrations, 1 X day, NS.	Psoriasis vulgaris. ICAM-1↓, CD 3↓, HLA-DR↓ (T>C); KI 67↓, Keratin 6↓, and Keratin 16↓(T≈C); biopsy (NS)	11 (no reasons); AEs: NS	SG: U AC: U BPt: H BPl: U BOS: L IOD: U SOR: L
Bernstein, S. 2006; US & Canada; 12 weeks; NS	T:100/97, C:100/74; T:51/49, C:42/58; T:48.3±13.7, (18-80) yrs C:48.3±14.0,(18-80) yrs; 2 groups, double-blind, vehicle-control.	T: psoberine emulsion cream (extract of *Mahonia aqulifolium* 10%), 2 X day, manufactured by IGI, Inc, NJ; Canadian Custom Packaging , Canada). C: vehicle cream (without active component), 2 X day, manufacturer same as for Test.	Plaque psoriasis (mild to moderate). PASI change T>C (T:-3.58±3.47, (-11 to 3), C:-2.22±3.25, (-11.9 to 4, p=0.0095) QLI change T>C (T:25.5±28.76, (-41 to 98), C:15.1±22.45, (-31 to 81, p=0.0186)	T:3, C:26; AEs: No SAE, T: staining (1), C: rash (1) and burning (2)	SG: U AC: U BPt: L BPl: L BOS: U IOD: L SOR: H
Brown, A. C. 2005; Hawaii (Oahu), USA; 12 weeks; NS	T:15/13, C:15/11; T: 5/8, C:7/4; (18-78)/(20-75) yrs; 2 groups, double-blind, placebo-control.	T: Kukui nut oil (*Aleurites moluccana* 9.10% saturated fat, 21.20% monounsaturated fat, 69.70 polyunsaturated fat, plus 102 IU/100 g of vitamin E, and 2.7 mg/100g of vitamin C) Vitamins E & C were added as antioxidant preservatives for the polyunsaturated fats. Used on target plaque/lesions: just enough to moisten lesions, 3 X day	Mild stable plaque psoriasis. Photographs of target lesions: PASI T≈C (p=0.468), Global Severity of Psoriasis Scale T≈C (p>0.05),	T:2, C:4 (reasons given); AEs: No	SG: U AC: U BPt: L BPl: U BOS: L IOD: L SOR: H

		(after showering, at noon, and before bed), also on remaining lesions. Oil left on for 8 hrs. C: mineral oil (NS). Used on target plaque/lesions: just enough to moisten lesions, 3 X day Application same as for Test.			
Choonhakarn, C. 2010; Khon Kaen, Thailand; 8 weeks; NS	T:40/37, C:40/38; T:17/20, C:19/19; T:43.4 ± 11.2, (27–65) yrs, C:44.2 ± 13.0, (23–71) yrs; 2 groups, double-blind, active-control	T: *Aloe vera* cream (70% *aloe* mucilage). 2 X day, no emollient was used. Prepared by Faculty of Pharmaceutical Sciences, Khon Kaen University. C: 0.1% triamcinolone acetonide cream. Same application & manufacturer as the Test	Plaque psoriasis (< 10% of body surface). PASI change T>C (T:6.6±2.1, C:7.7±2.3, p=0.0237) DLQI change T≈C (T:5.8±2.0, C:6.1±2.1, p=0.5497)	T:3, C:2 lost during follow-up; AEs: No SAE, T: stinging and itching (6), C: no significant complaint	SG: L AC: L BPt: L BPl: L BOS: U IOD: U SOR: L
Gulliver, W. P., 2005 (study 2); NY, US; 6 months; NS	32/30; NS; NS; 1 group, single blind, active control	T: *Mahonia aqulifolium* cream (0.1% berberine). Manufactured by Prime Pharmaceutical Corporation. C: calcipotriol cream & fluticasone propionate	Mild to moderate bilateral psoriasis, half-body. Patient's ratings of T: 84% as good to excellent; patient's ratings of the comparison with C: 63% as equal to better than C	2 (did not return); AEs: No	SG: U AC: U BPt: L BPl: U BOS: L IOD: U SOR: U
Gulliver, W. P., 2005 (study 3); Niagara Falls, Ontario, Canada; 4 weeks; NS	33/33; NS; NS; 2 groups, single blind, active control	T: 1) *Mahonia aqulifolium* cream (0.1% berberine): manufactured by Prime Pharmaceutical Corporation. 2) Calcipotriol cream plus tazarotene gel. C: vehicle cream. (NS).	Mild to moderate psoriasis. photographs, physician ratings T>C (all participants)	None; AEs: seem not to be related the treatment	SG: U AC: U BPt: L BPl: U BOS: U IOD: L SOR: H
Lin, Y-K., 2007; Taoyuan & Taipei, China; 8 weeks; 3 months	14/10; M/F:11/3; 35.8±10.4, (21-54) yrs; half-body, 1 group, vehicle-control	T: *Indigo naturalis* ointment (20% *Baphicacanthus cusia* powder, 80% vehicle ointment). Areas of target lesions were measured and the *Indigo naturalis* ointment was applied with 1g/100cm^2 each time, 1	Recalcitrant plaque psoriasis. Psoriasis severity index (PSI): T<C (p<0.05); Clearance % of target lesions: T>C	4 (non compliance); AEs: short term itching (2)	SG: U AC: U BPt: U BPl: L BOS: U IOD: L

		X day. Wash hands thoroughly between each application. Sample was identified and provided by the Chinese Medicine Pharmacy of the authors' institution. C: vehicle ointment: (25% petroleum jelly, 30% yellow wax, and 45% olive oil). Application same as for Test.	($p<0.05$); Histological examination of skin biopsies, and Representative photos: T better than C		SOR: H
Lin, Y-K., 2008; Taoyuan & Taipei, China; 12 weeks; NS	42/34; M/F:32/10; 34.6±11.5 (18-58) yrs; half-body,1 group, vehicle-control, observer-blind	T: *Indigo naturalis* ointment (1.4% *Strobilanthes formosanus* containing 0.16% indirubin): *Indigo naturalis* powder and vehicle mixed in the ratio of 1:10. Ointment was prepared by a research pharmacist who knew the treatment assignment. 1 fingertip unit=0.5g per100cm^2 applied to lesions on one side. Wash hands thoroughly between each application. C: Vehicle ointment (petroleum jelly: yellow wax: olive oil = 5:6:9). Ointment was prepared by a research pharmacist who knew the treatment assignment. Application same as for Test.	Recalcitrant psoriasis. Scores (scaling, erythema, induration, and sum): T<C ($p<0.001$) Clearing percentage of target plaque: T>C ($p<0.001$); Clinical efficacy: T>C ($p<0.001$)	8 (3 due to slow effect, 3 due to work, 2 lost to follow-up); AEs: no SAE T: itching (4), C: NS Liver & Kidney function normal	SG: U AC: L BPt: H BPl: U BOS: L IOD: L SOR: L
Paulsen, E., 2005; Odense, Denmark; 4 weeks; 1-2 months	41/40; M/F:26/14; 44, (23-77) yrs; half-body, 1 group, double-blind, vehicle-control	T: *Aloe vera* gel (98% *Aloe vera* leaf gel, with less than 100 p.p.m. of anthraquinones, and the additives xanthan gum, potassium sorbate, sodium benzoate, sodium sulphite & citric acid). 2 X day. Extracted from Mexican plantations by Aloe Vera Group ApS, Søborg, Denmark. C: vehicle gel: same ingredients as Test except Aloe vera replaced by water. 2 X day.	Slight to moderate psoriasis vulgaris. PASI of target lesion: reduction of symptom scores (erythema, infiltration & desquamation): T<C ($p=0.0197$)	1 dropout in week 2; AEs: no SAE. Local AEs (n=22), most were dry skin, some were stinging, soreness, or fissures, incl. 2 erythema (one together with a slight tingling sensation) in T grp. C: some cases of tingling & tightness of the skin.	SG: L AC: L BPt: L BPl: L BOS: U IOD: L SOR: H

Syed, T. A., 1996; Punjab, Pakistan; 4 weeks; 8 months	T:30/30, C:30/30; T:18/12, C:18/12; T:25.9, C:25.2; 2 groups, double-blind, vehicle-control	T: *Aloe vera* extract cream (0.5% *Aloe vera* extract by weight in a hydrophilic vehicle cream containing mineral oil and castor oil (B.P.)). 3 X day for 5 consecutive days (<=15 times/week), avoiding occlusion or exposure of lesions to sunlight. Prepared as 100g tubes by Department of Chemistry, University of the Punjab, Lahore. C: vehicle cream: same ingredients as left without Aloe vera, in identical 100g tubes. Application & manufacturer same as for Test.	Slight to moderate chronic plaque psoriasis. Cured rate: T>C ($p<0.001$); Clearing of plaques: T>C ($p<0.001$); Mean PASI: substantial decrease in T (9.7→2.2) vs C (8.9→8.2). Laboratory tests: complete blood cell count & urinalysis, and biopsy analysis	No; AEs: no	SG: U AC: U BPt: L BPl: L BOS: U IOD: L SOR: H
Wang, A.M., 1998; Hubei, China; 60 days; NS	T1: 40/40, T2: 86/86, T3: 38/38, C: 20/20; M/F (total): 108/76; Age (total): 10-30 yrs: 80, 30-50 yrs: 41, > 50 yrs: 33; 4 groups, vehicle -controls	T1: *Camptotheca acuminata* nut thin gel*: (*Camptotheca acuminata* nut extract 20g, ethanol 5g, glycerol 5g, Sodium hydroxymethyl cellulose 4g, polyvinyl alcohol (PVA-124) 3g) T2: *Camptotheca acuminata* nut ointment: (*Camptotheca acuminata* nut extract 20g, petroleum jelly 72g, lanolin 8g). T3: *Camptotheca acuminata* nut tincture: (dried *Camptotheca acuminata* nut 100g, Dimethyl sulfoxide (DMSO) 250ml, 75% ethanol 750ml). All 2 X day (interval 12 hrs) (excluding broken skin and mucous membranes). C: vehicle thin gel (ethanol 5g, glycerol 5g, Sodium hydroxymethyl cellulose 4g, polyvinyl alcohol (PVA-124) 3g). 2 X day (interval 12 hrs).	Psoriasis vulgaris. Reduction of lesion area: T1>C ($\chi2 =17.96$, $p<0.01$), T1>T2 ($\chi2 =4.16$, $p<0.05$), T1>T3 ($\chi2 =6.25$, $p<0.05$), T2≈T3 ($\chi2 =0.64$, $p>0.05$)	None; NS	SG: U AC: U BPt: H BPl: U BOS: U IOD: L SOR: L
Wiesenauer,	82/80;	T: Ointment (10% *Mahonia*	Psoriasis vulgaris .	2 dropouts;	SG: U

M., 1996; Germany; 4 weeks (median); NS	M/F: 43/39; 47±14, (16-85) yrs; 1 group, double-blind, vehicle -control, multi-centre	*aqulifolium* bark extract) Ointment base (anhydrous lanolin, paraffin, wool wax alcohols, cetylstearyl alcohol and white petroleum jelly). Massage ointment on afflicted area 2-3 X day and at night (wrapped in bandages) for 8 weeks. Prepared in 100g/tube according to German Homeopathic Pharmacopoeia (HAB1). C: Ointment base (anhydrous lanolin, paraffin, wool wax alcohols, cetylstearyl alcohol and white petroleum jelly). Applied same as for Test.	3 point global symptom scale. Agreement of assessments of efficacy by Patient (T>C, p=0.008) & physician (T≈C, p=0.013)	AEs: allergic reaction (1), strong itching (1), burning & irritation of skin (2) no serious AEs	AC: U BPt: U BPl: U BOS: U IOD: L SOR: L

T: treatment group, C: control group, R/A: registration/analysis, M/F: male/female, NS: not stated, WM: Western medicine, sys: systemic, yrs: years, wks: weeks, mins: minutes, RCT: randomised clinical trial, PASI: Psoriasis Area and Severity Index
*Note that this gel preparation was mistranslated as 'lacquer' in the original paper.

Risk of Bias Categories
SG: sequence generation, AC: allocation concealment, BPt: blinding of participants, BPl: blinding of personnel, BOS: blinding of outcome assessment, IOD: incomplete outcome data, SOR: selective outcome reporting

Risk of Bias Judgements
L: low risk, U: Unclear risk, H: High risk

Five types of single-herb preparations were tested. They were obtained from the following: *Mahonia aquifolium* (5 studies), *Aloe vera* (3 studies), indigo naturalis (2 studies), kukui nut oil (1 study) and 3 different preparations of *Camptotheca acuminate* nut (1 study).

***M. aquifolium* (5 RCTs)**

In a double-blind half-body placebo-control RCT, Wiesenauer and Ludtke (1996) analysed the results of treatment with an ointment containing 10% *M. aquifolium* bark extract using the ointment base as the control. The 2 preparations were applied to symmetrically distributed lesions. The test ointment was more effective than the ointment base, as judged by intention-to-treat analysis. However, a large proportion of patients and some physicians stated that the treatment had been ineffective. The probability of symptom improvement as a result of this treatment appeared to be 3 to 4 times higher in moderately severe cases than in mild cases (219).

In 1999, in another half-body RCT, Augustin *et al.* (209) tested the *M. aquifolium* ointment and dithranol. Their study examined the effect of these two treatments on cellular cutaneous immune mechanisms and hyperproliferation of keratinocytes (keratin 6, keratin 15 and Ki-67), adhesion molecules (ICAM-1) and other activation markers (HLA-DR). The researchers used a pre- and post-intervention blinded assessment of biopsy performed by 2 independent physicians (209). Both the treatments reduced epidermal and dermal T-cell infiltration; however, the effect was less pronounced for the *Mahonia* ointment. The authors reported a marked regression of proliferation and adhesion markers caused by the *Mahonia* ointment and stated that both treatments were effective. However, dithranol provides better results than the *Mahonia* ointment.

Gulliver and Donsky conducted 3 studies testing the use of *M. aquifolium* cream in psoriasis (213). The first was a safety study, and the other 2 were RCTs using different half-body designs. In the second study, all 32 patients applied *Mahonia* cream to 1 of the bilateral lesions and a similar cream, containing calcipotriol and fluticasone propionate, to the other lesion. Of the 30 patients who completed the study, 25 assessed *Mahonia* cream as good to excellent; however, 3 patients did not respond to the cream. In the third study, 33 patients with bilateral lesions were randomly assigned to 1 of 2 groups. In 1 group, *Mahonia* cream was used on the lesion on 1 side, while the vehicle cream was applied to the lesion on the

opposite side. In the second group, a cream containing calcipotriol and tazarotene gel was used on 1 side and the vehicle cream was on the other side. The authors reported that participants had been blinded. Photographs of the plaques were evaluated by physicians. In both the treatments, the thickness and redness of the plaques diminished over the 4-week therapy. The study reports that the results obtained using *Mahonia* cream are as good or better than, but not substantially superior to, the topical pharmaceuticals (213).

In a double-blind placebo-controlled RCT, Bernstein *et al*. examined the efficacy of Psoberine®, a commercial cream containing the extract of *M. aquifolium*, at 6 sites in the USA and Canada (210). A group of 200 patients with mild to moderate plaque psoriasis (but no administration of anti-psoriatic medications during the previous 28 days) was enrolled in the study. The patients were randomly assigned to 1 of the 2 groups: 1 to use the *Mahonia* extract cream and the other to use the vehicle cream as placebo. The creams were applied to a selected area twice a day for 12 weeks. Only 171 patients completed the study; 'no response' was the main reason for discontinuation. Intention-to-treat analysis (worst case) of PASI scores revealed a statistically significant reduction in the scores. The group using *Mahonia* cream showed mean reduction of 3.39 from 6.93 at baseline. QLI scores also improved significantly for the patients using *Mahonia* cream. Therefore, the authors concluded that *Mahonia* cream was a well-tolerated and satisfactory treatment for mild to moderate psoriasis.

***A. vera* (3 RCTs)**

In a 60-participant double-blind placebo-controlled study, Syed *et al.* compared a cream containing 0.5% *A. vera* extract with the vehicle cream for treating moderate chronic plaque psoriasis (217). After a month, there was a significant improvement in PASI scores in the *A. vera* group (baseline mean: 9.3, endpoint mean: 2.2). No medication-related adverse events were reported in the study, either local or systemic, and there were no cases of hypersensitivity or dermatitis. The authors concluded that the *A. vera* preparation was well tolerated and appeared to be remarkably effective.

In a double-blind placebo-controlled half-body study, Paulsen *et al.* tested a commercial *A. vera* gel, using the vehicle gel as the control (216). Forty patients with stable symmetrical bilateral lesions used *A. vera* or placebo gel on a right- or left-side lesion. Emollients, petroleum jelly, salicylic acid and tar-containing shampoo were allowed for other lesions.

The authors found that modified PASI scores were reduced in both the groups. However, the effect of placebo was stronger than that of the commercial *A. vera* gel at the end of treatment (but not during the follow-up). Some skin irritation associated with dryness was reported in both the groups; however, there were no serious adverse events.

In a double-blind parallel-group RCT, Choonhakarn *et al.* compared treatment with *A. vera* cream and 0.1% triamcinolone acetonide cream (212). The study recruited 80 patients with chronic plaque psoriasis. The participants were requested not to take any topical or systemic anti-psoriatic treatments for 4 weeks prior to the study. The treatment was administered twice a day for 8 weeks. Both the groups improved their PASI and DLQI, with a significantly greater improvement in PASI in the *A. vera* group. No inter-group difference was observed for DLQI. The authors concluded that *A. vera* cream was safe and its efficacy was at least similar to that of triamcinolone acetonide cream.

***I. naturalis* (2 RCTs)**

In a 14-patient blinded placebo-controlled study, Lin *et al*. compared the indigo naturalis ointment (extract of *Baphicacanthus cusia*) with the vehicle ointment, applied to comparable bilateral lesions (215). Outcome measures included PSI, percentage clearance of target lesions and histological examination of skin biopsies. After 8 weeks, the clinical scores were reduced in the indigo group; this decline was closely correlated with the length of treatment. Skin biopsies revealed a marked decrease in the epidermal thickness in the indigo group in comparison with the vehicle ointment group. There were no adverse events; however, short-term itching was reported by 2 participants.

The same research group also examined another indigo ointment, based on a *Strobilanthes formosanus* preparation, which contained 1.4% indigo and 0.16% indirubin. The study used the vehicle ointment as the control (214). The outcome measures included the scaling score, erythaema score, induration score, sum of these scores and area of target plaque based on photographs. The comparisons were conducted by blinded assessors. Itching was reported by 4 patients for 2 days after starting the indigo ointment treatment; 3 patients withdrew because of no response and 5 failed to complete the treatment for other reasons. Intention-to-treat analysis revealed significant improvements in the summation score weighted by the lesion area, scaling, erythaema and induration in the indigo group. The score improvement was positively correlated with the duration of the treatment. The placebo

ointment also resulted in some improvements but to a lesser degree. Blood test results in both indigo studies showed normal liver and kidney functions (214, 215).

Kukui nut oil (1 RCT)

In a 30-participant double-blind parallel-group placebo-controlled study, Brown *et al.* compared kukui nut oil (a Hawaiian traditional medicine derived from *Aleurites moluccana)* with a mineral oil in the treatment of mild, stable plaque psoriasis (211). Outcomes included PASI and Global Severity of Psoriasis Scale, assessed on the basis of photographic evidence. Both the groups showed improvement; however, no significant differences were observed between the groups in terms of PASI or Global Severity of Psoriasis Scale. However, a number of patients became unblinded (n = 13), and there were more dropouts in the placebo group than in the test group (11 out of 13).

C. acuminata nut preparations (1 RCT)

In an open-label parallel-group study, Wang *et al.* (1998) tested the efficacy of 3 preparations of *C. acuminata* nut (thin gel, n = 40; ointment, n = 86 and tincture, n = 38) in comparison with that of the thin gel used as placebo (n = 20) (218). In terms of the efficacy rate based on reduction of the lesion area, the *Camptotheca* gel preparation resulted in a significantly greater improvement in comparison with the 2 other *Camptotheca* preparations (which did not differ) and the placebo gel. The tincture caused some skin irritation and the ointment stained clothes. No side effects were reported for the gel. The authors concluded that the thin gel was superior to the other 2 preparations.

6.1.4 Methodological assessment

The study quality with risk of bias is reported in Table 6.1. All the authors stated that their studies were ‘randomised’ or used a similar expression. The randomisation sequence generation method was reported in 2 of the studies; these studies were assessed as ‘low’ risk of bias for this item (212, 216). ‘Unclear’ risk of bias was assigned to the remaining 10 studies. The allocation concealment method was described by 3 studies (212, 214, 216); these were judged as having ‘low’ risk in this category, while other studies were judged as having ‘unclear’ risk of bias.

Blinding of participants failed in 3 studies. These studies applied clearly different interventions for the 2 groups (209, 214, 218) and were judged as having 'high' risk of bias. Two studies did not provide details of blinding (215, 219), and their risks of bias were judged as 'unclear'. The remaining 7 studies used appropriate methods of blinding and were judged as having 'low' risk on blinding of participants. In 5 of the studies, appropriate procedures prevented physicians or investigators from identifying the groups; therefore, they were judged as having 'low' risk of bias in the domain of personnel blinding (210, 212, 215-217). The methods for blinding of outcome assessors were described in 4 studies (209, 211, 213, 214); these were judged as having 'low' risk of bias for this item.

Because the dropout reasons were not reported in 4 studies, they were judged as having 'unclear' risk of bias for incomplete outcome reporting (209, 212, 213, 219). The 8 studies that reported the reasons for dropouts or stated that there were no dropouts were judged as having 'low' risk. In 5 studies, not all data for outcomes stated in the methods were reported in the results; these were judged as having 'high' risk of selective data reporting (210, 211, 215-217). One study was judged as 'unclear' (213), and the remaining studies were judged as having 'low' risk of bias in this category.

6.1.5 Meta-analysis

After careful scrutiny of available data, we decided that 7 of the examined studies contained data suitable for meta-analysis (210, 212, 214, 216-219). Outcome measures included clinical efficacy (n = 6) (212, 214, 216-219), symptom score (n = 1) (214), PASI (n = 1) (212), PASI change (n = 1) (210, 212), DLQI (n = 1) (212) and DLQI change (n = 1) (212) (Table 6.2).

Table 6.2 Results of meta-analyses for clinical efficacy, PASI, DLQI and symptom score [adapted from Deng 2013 (159)]

Outcomes, **RCT No. (overall sample size)**	**First author,** **Publication year**	***meta-analysis* on endpoint results**	**Incidence % (n/N) or** **MD ± SD**	**RD (%)**
Clinical efficacy				
Indigo vs placebo, 1 (84)	Lin 2008	4.83 [2.24, 10.42] RE*	T: 69.0% (29/42) C: 14.3% (6/42)	54.7
Aloe vera vs placebo, 1 (82)	Paulsen 2005	0.67 [0.20, 2.19] RE	T: 9.8% (4/41) C: 14.6% (6/41)	-4.8
Aloe vera vs placebo, 1 (60)	Syed 1996	12.50 [3.25, 48.14] RE*	T: 83.3% (25/30) C: 6.7% (2/30)	76.6
Aloe vera vs placebo (pooled), 2 (142)		2.84 [0.16, 50.12] I^2 =90% RE	T: 40.8% (29/71) C: 11.3% (8/71)	29.5
Camptotheca tincture vs placebo†, 1 (58)	Wang 1998	6.05 [1.59, 23.11] RE*	T: 60.5% (23/38) C: 10.0% (2/20)	50.5
Camptotheca thin gel vs placebo, 1 (60)	Wang 1998	8.75 [2.34, 32.75] RE*	T: 87.5% (35/40) C: 10.0% (2/20)	77.5
Camptotheca ointment vs placebo†, 1 (106)	Wang 1998	6.51 [1.73, 24.47] RE*	T: 65.1% (56/86) C: 10.0% (2/20)	55.1
Camptotheca vs placebo (pooled), 1 (224)		7.02 [3.26, 15.12] I^2 =0% RE*	T: 69.5% (114/164) C: 10.0% (6/60)	59.5
Mahonia vs placebo, 1 (164)	Wiesenauer 1996	1.71 [1.02, 2.85] RE*	T: 35.4% (29/82) C: 20.7% (17/82)	14.7
HM vs placebo (pooled), 5 (450)		3.37 [1.36, 8.33] I^2 =78% RE*	T: 51.9% (122/235) C: 15.3% (33/215)	41.5
Aloe vera vs pharm., 1 (80)	Choonhakarn 2010	0.90 [0.67, 1.21] RE	T: 65.0% (26/40) C: 72.5% (29/40)	-7.5
PASI score				
Aloe vera vs pharm.†, 1 (75)	Choonhakarn 2010	-0.40 [-1.26, 0.46] FE	T: before 11.6±2.9, after 3.9±1.7 C: before 10.9±3.1, after 4.3±2.1	NA
PASI change				
Mahonia vs placebo†, 1 (200)	Bernstein 2006	-3.30 [-4.48,-2.12] FE*	NA	

DLQI				
Aloe vera vs pharm.†, 1 (75)	Choonhakarn 2010	0.20 [-0.30, 0.70] FE	T: before 8.6±1.7, after 2.5±1.2 C: before 8.1±1.8, after 2.3±1.0	NA
QLI change				
Mahonia vs placebo†, 1 (199)	Bernstein 2006	27.48 [17.24,37.72] FE*	NA	
Symptom score				
Scaling (*Indigo naturalis* vs placebo)†, 1 (68)	Lin 2008	-2.20 [-2.93, -1.47] FE*	T: before 6.8±1.31, after 1.5±1.46 C: before 6.7±1.31, after 3.7±1.60	NA
Erythema (*Indigo naturalis* vs placebo)†, 1 (68)	Lin 2008	-2.30 [-3.04, -1.56] FE*	T: before 6.0±1.42, after 2.6±1.60 C: before 6.0±1.40, after 4.9±1.50	NA
Induration (*Indigo naturalis* vs placebo)†, 1 (68)	Lin 2008	-2.00 [-2.68, -1.32] FE*	T: before 6.1±1.28, after 2.2±1.49 C: before 6.0±1.32, after 4.2±1.37	NA
Summation (*Indigo naturalis* vs placebo)†, 1 (68)	Lin 2008	-6.50 [-8.45, -4.55] FE*	T: before 18.9±2.97, after 6.3±4.28 C: before 18.7±3.08, after 12.8±3.92	NA

T: test group; C: control group; RR: risk ratio; N: total number of participants in group; n: number of participants in sub-group; I^2: test of heterogeneity of meta-analysis of pooled data, over 50% represents substantial heterogeneity; MD: mean difference; SD standard deviation; RD: Risk difference; NA: not applicable; RE: random-effect model; FE: fixed-effect model

HM: herbal medicine; Pharm.: pharmacotherapy; QLI: Quality of Life Index; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index

*Significantly different; †Not included in pooling

Clinical efficacy

Different studies used different systems for classifying clinical efficacy and PASI reduction. Therefore, our clinical efficacy assessment only included cases with an efficacy rate of 50% or above or PASI reduction of 50% or more (185). One study also reported the numbers of participants whose condition improved (219). Results were analysed using risk ratio (RR) and a random-effect model. In meta-analysis, a higher score indicates greater efficacy. Of the 6 studies suitable for meta-analysis, 5 compared a herbal extract with the vehicle as placebo (214, 216-219) and 1 used an active control (212).

The *Indigo naturalis* ointment had superior efficacy than placebo (RR 4.83, 95% CI: 2.24–10.42) in the study of Lin *et al*. (2008), similar to the findings with the *M. aquifolium* ointment (RR 1.87, 95% CI: 2.44–8.89) in the report of Wiesenauer *et al.* (1996). The *A. vera* preparation was significantly more effective than placebo in the study of Syed et ak, (1996) (RR 12.50, 95% CI: 3.25–48.14); however, there was no difference between experimental and control groups in the study by Paulson (2005) (RR 0.67, 95% CI: 0.20–2.19) (Fig. 6.2).

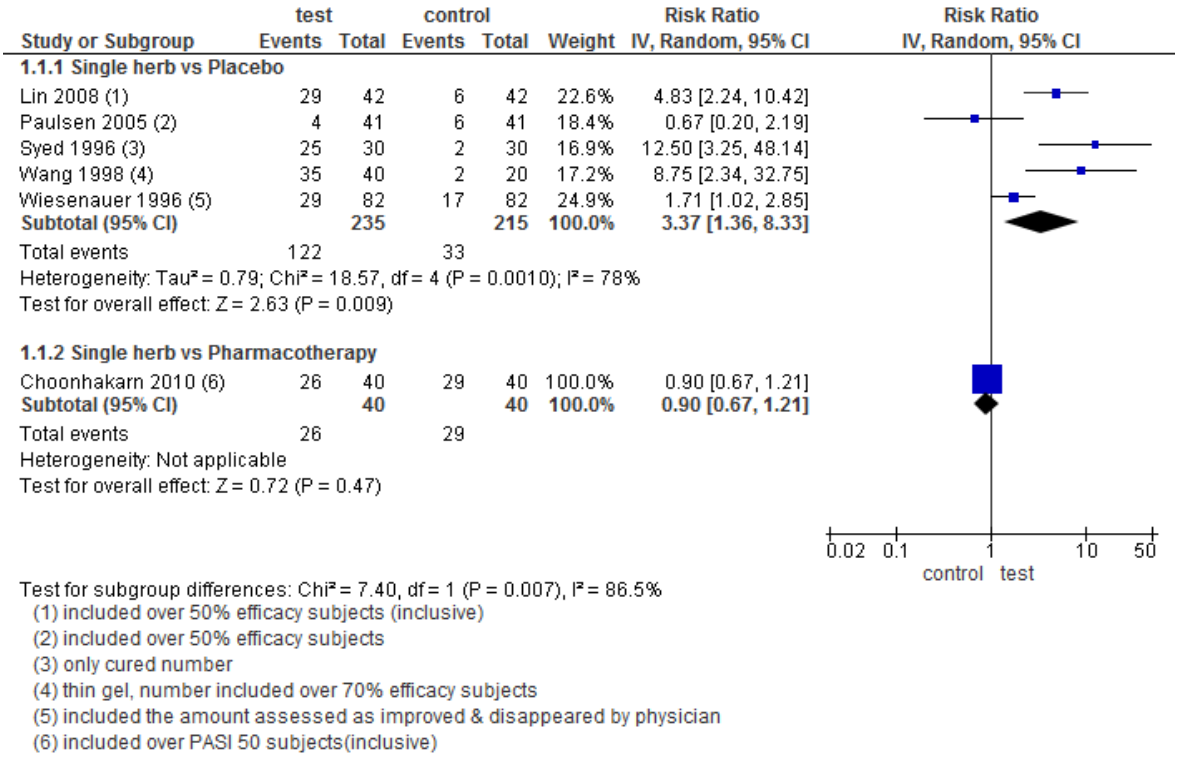


Fig. 6.2 Forest plot of clinical efficacy of single herb used topically for psoriasis

The three different *Camptotheca* preparations, namely ointment (RR 6.51, 95% CI: 1.73–24.47), tincture (RR 6.05, 95% CI: 1.59–23.11) and thin gel (RR 8.75, 95% CI: 2.34–32.75), showed a significantly greater effect than placebo (Fig. 6.2). The thin gel was superior to the ointment (RR 1.34, 95% CI: 1.11–1.63) and to the tincture (RR 1.45, 95% CI: 1.09–1.92); however, there was no significant difference between the ointment and tincture (RR 1.08, 95% CI: 0.80–1.45). This was in accordance with conclusions of the authors.

The pooled data for this group of 5 studies showed a difference between clinical efficacy of the plant extracts and their vehicles (used as placebo) (RR 3.37, 95% CI: 1.36–8.33). However, the heterogeneity was high (78%), and sensitivity analyses could not identify an optimal sub-group of studies. No significant difference was observed between the efficacy of *A. vera* and triamcinolone acetonide preparations (RR 0.90, 95% CI: 0.67–1.21, p = 0.47) (Fig. 6. 2).

Other outcomes

No significant differences were observed between PASI (MD −0.40, 95% CI: −1.26, 0.46) or DLQI (MD 0.20, 95% CI: −0.30, 0.70) values in the experimental and control groups in the study of Choonhakarn *et al.* (2010). Lin *et al.* (2008) reported significant improvements in symptom scores for scaling, erythaema, induration and summation of symptoms (Table Ch. 6.2).

6.1.6 Adverse events (AEs)

There were 11 studies that discussed AEs, and 1 study did not provide any information (209). Three studies reported that there were no adverse effects (211, 213, 217). One *Mahonia* study reported bilateral exacerbations, which the authors thought unlikely to be related to the *Mahonia* (213). Of the 7 remaining studies, 5 stated that there were no severe AEs (210, 212, 214, 216, 218). In the studies that reported AEs, the most frequent were local skin irritations or other problems described as staining, itching, dryness and burning or tingling sensation.

6.1.7 Summary

In 10 studies, the single-herb preparations were shown to be effective; however, the data in 6 of those studies (209-211, 213, 215) were not suitable for meta-analysis. Inconclusive results were reported for kukui nut oil treatment (211), and negative results were found in 1 study of

A. vera preparations (216). Meta-analyses produced conflicting results for clinical efficacy in 2 studies comparing the effects of *A. vera* and placebo (216, 217). However, the results of the study of Paulsen *et al.* (2005) may have been confounded by the concurrent use of other medications. A well-designed, relatively recent study by Choonhakarn *et al.* (2010) showed that treatment with *A. vera* cream have similar benefits to treatment with 0.1% triamcinolone acetonide cream (Fig. 2). The 2 RCTs of indigo naturalis (214, 215) reported the efficacy of this remedy in plaque psoriasis, and a more recent RCT comparing 2 indigo preparations reported similar results (220). A number of case reports have also reported beneficial effects of indigo (221, 222), and a recent uncontrolled study of 32 patients with nail psoriasis found a decrease in the nail PSI after 24 weeks of treatment (223). However, there has been no independent confirmation of these results. The efficacy of *C. acuminata* nut preparations was higher than in the placebo group; however, the study was not blind (218). All the studies of *M. aquifolium* (209, 210, 213, 219) reported positive effects and were conducted by different research groups. However, the reports showed inadequacies, and variation in outcome data precluded pooling and assessment of the bias.

For indigo, *Mahonia* and *Camptotheca* trials, the clinical findings have been confirmed by experimental studies. However, further research is required to characterise the compounds derived from or based on these herbs. The clinical trial data, obtained from several studies, have provided some evidence of potential benefits of the topical use *M. aquifolium,* indigo naturalis and *A. vera* preparations in the management of mild to moderate plaque psoriasis. The preparations used did not appear to produce any serious AEs; however, the duration of indigo naturalis and *A. vera* treatments was relatively short. However, most studies were rather small and the methodology had some weaknesses; therefore, definitive conclusions cannot be made. Because the effects cannot be accurately measured, the assessment of the clinical relevance of these studies remains difficult.

6.2 Results of systematic review 3: Herbal formula for the external management of psoriasis: A systematic review with meta-analysis of RCTs

6.2.1 Introduction

Traditional HM tends to combine various medicinal herb recipes or formulae, which may enhance the desired therapeutic effects and avoid side effects. Such preparations are often administered internally; however, many are used topically in the form of washes, baths,

sprays, tinctures, powders, ointments, creams, gels and cataplasms (224). Here we review clinical studies of the efficacy and safety of such multi-ingredient herbal formulae in the external management of psoriasis vulgaris. This study identifies some individual herbs showing promising efficacy. We also examine the experimental evidence of activities relevant to psoriasis for identifying possible new directions for drug discovery and development (167).

6.2.2 Method

We evaluated several reviews describing the role of externally applied HM in the management of psoriasis (35, 36, 48, 157, 164). To fund the relevant publications, we searched the following databases: EMBASE, PubMed, Cochrane Library, CNKI Database and CQVIP (up to September 2012). Search terms comprised 3 groups: clinical condition, intervention and study type, with adjustments for different databases (see Chapter 4 for lists of terms). We also searched reference lists in review articles.

Herbal formulae were defined as preparations of multiple herbs, which mainly contain plant material but may also include natural products of animal or mineral origin. Dead Sea cure, homeopathy, ultraviolet radiation therapy, fish and animal oils and specific vitamin and/or mineral therapies were excluded. Only studies that investigated topical herbal formulae in experimental intervention were included, excluding single herbs and treatments combining plant preparations with topical APP. Studies employing identical systemic co-interventions using herbal medicines, vitamins, minerals or pharmaceuticals in both experimental and control groups were included.

Two researchers (SD & BHM) conducted searches, extracted data and assessed risk of bias (171). Disagreements were resolved by discussions with a third researcher (ALZ) if agreement could not be reached. A flowchart of the study selection procedure is presented in Fig. 6.3 (132). Data were analysed using RevMan 5.1 with RR with 95% CI employing fixed- or random-effect models depending on heterogeneity (172).

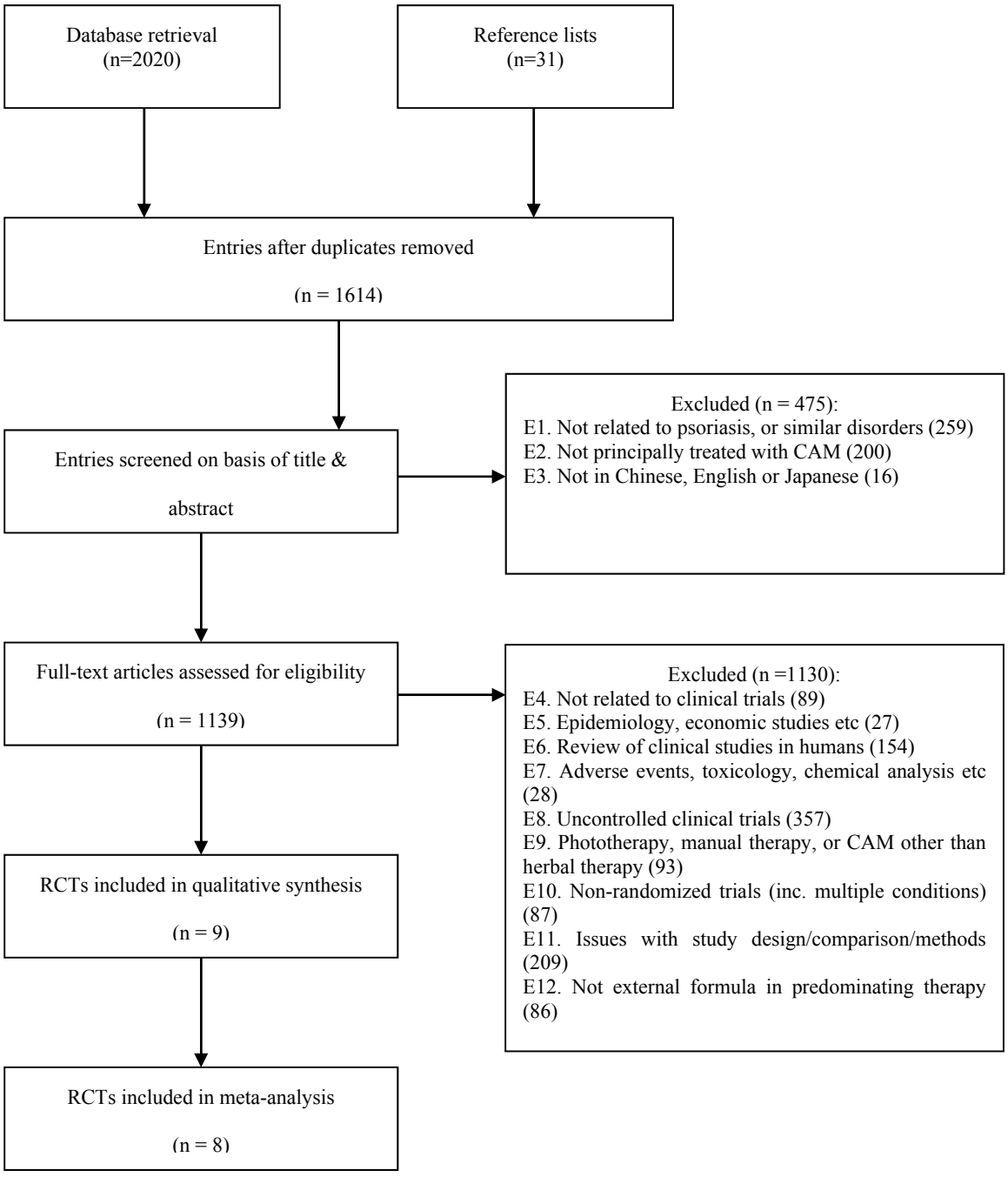


Fig. 6.3 Flow chart of the selection procedure of randomised controlled trials (RCTs) on external formula for treating psoriasis [adapted from Deng 2013 (158)]

6.2.3 Results

Database searches yielded 2,020 potentially relevant articles, and 31 studies were identified using reference lists. After the removal of duplicates, the remaining 1,614 records were screened and the full text was obtained for 1,139 articles. Nine RCTs met all the inclusion criteria (225-233).

Eight of the included RCTs were conducted in China and 1 in Finland; 2 were published in English and 7 in Chinese. Altogether, 1,214 participants completed the 9 studies (Table Ch. 6.3). The largest study enrolled 376 participants (225) and the smallest enrolled 42 participants (226). The criteria for inclusion and/or exclusion were provided in 8 of the studies (225-228, 230, 231, 233, 234), and 7 studies stated the diagnostic criteria for inclusion (225, 228-233). The study duration ranged from 2 weeks (1 study) to 12 weeks (1 study), with a median of 4 weeks (2 studies).

Three studies compared the effect of topical HM with that of topical placebo, and 5 studies used topical APP as the comparator (Table 6.4). One study compared topical HM with topical placebo as well as with APP (228). APPs included clobestasol (225, 231), fluocinonide (227), calcipotriol (228), anthralin (229) and tretinoin (233). Outcome measures included the PASI score (n = 5) (225, 229, 231-233) and modified PASI score (n = 2) (228, 230). Various psoriatic symptom scores were also used: 2 studies provided scores for scaling, pruritus/itching, erythaema and induration (226, 227), 2 studies also included a 'lesion area' score (228, 230) and 1 study measured 'itching' as a symptom (232). In the study by Zhou *et al*. (2009), the outcomes measured also included AEs and safety. Each study provided an assessment of the overall clinical efficacy on the basis of the abovementioned outcome measures; however, the methods of calculation were variable.

The topical formulae used in the studies were in the form of cream/ointment (4 studies), spraying agent (1study), tincture (1study), bath decoction (1study) and cataplasm (1 study). One study did not specify the form of preparation. Nine different HM formulae were assessed: Liubai Baibi (cream/cataplasm), Qinbai Ruangao (conventional/fine ointment), oleum horwathiensis spraying agent (Psoricur®), Queyin tincture, compound E-Bei ointment, Herbal Bath Formula (No. 1 or No. 2), New Pulian Ointment and Xiaoxuanling formula.

Two studies used 3 experimental groups (228, 230), and the remaining 7 studies used 2 groups. In 2 studies, oral pharmaceuticals were used in addition to the topical preparations (225, 231), and 3 studies applied oral herbal formulae as co-interventions (228, 230, 232). No co-intervention was employed in the remaining 4 studies (226, 227, 229, 233).

Table 6.3 Characteristics of the 9 studies on external herbal formulae for psoriasis [adapted from Deng 2013 (158)]

First author, Publication year, Location, Duration, Follow-up	**Sample size (R/A), Gender (M/F), Age: Mean ± SD (Range), RCT Design (T vs C)**	**Diagnosis, Outcome measures, Results**	**Dropouts, Adverse events (AEs)**	**Risk of Bias (SG, AC, BPt, BPl, BOA, IOD, SOR)**
Gao, W.Y. 2006; Qingdao, China; 8 weeks; NS	T:NS/192, C:NS/184; T:103/89, C:97/87; T:36.5, (18-65) yrs, C:33.5, (18-62) yrs; 2 groups, active-control: ext. HM + int. pharm. vs ext. APP + int. pharm.	Psoriasis vulgaris. Clinical efficacy based on reduction of PASI score T>C (χ^2 =36.15, p<0.01).	No details; AEs: No SAE, mild itching & burning (T=7, C=9)	SG: U AC: U BPt: U BPl: U BOA: U IOD: U SOR: L
Lassus, A., 1991; Helsinki, Finland; 12 weeks; 12 weeks	T: 25/19, C: 25/23; T: 9/10, C: 10/13; T: 43.1, (22-50) yrs, C: 42.5, (29-50) yrs; 2 groups, double-blind, vehicle-control： ext. HM vs ext. Placebo.	Chronic stable psoriasis. Changes in mean symptom severity: T>C Scaling (96.8% vs 75.5%), Pruritus (93.3% vs 54.3%), Erythema (58.1% vs 49.0%), Induration (68.0% vs 46.5%)	T: 6, C: 2; AEs: T: local irritation (1), C: NS	SG: U AC: U BPt: L BPl: L BOA: U IOD: L SOR: L
Lu, Y. P., 2004; Shenyang, China; 18 days; NS	T: 31/31, C: 22/22; T: 16/15, C: 12/10; NS; 2 groups, ext. HM vs ext. APP.	Stable psoriasis vulgaris. Clinical efficacy based on reduction of symptom score: T>C (p<0.05)	None; AEs: NS	SG: U AC: U BPt: U BPl: U BOA: U IOD: L SOR: L
Song, P., 2007; Beijing, China; 4 weeks; 0.5 years	T:60/60, C1(WM):30/29, C2(Placebo):30/29; T:39/21, C1(WM):19/11, C2(Placebo):16/14; T:42.4 ±12.5, C1(WM):37.0 ±10.1, C2(Placebo):38.8 ±10.5; 3 groups, block-randomized, active and vehicle controls,	Plaque psoriasis. Modified PASI scores: T<C2 (p<0.01), C1<C2 (p<0.01), T<C1 (p<0.01); Clinical efficacy: T>C2 (p<0.01), C1>C2 (p<0.01), T≈C1 (p>0.05), Single symptom scores: T<C2 (p<0.01), C1<C2 (p<0.01**);** Time to symptom improvement: 1) itching: T<C1/C2 (p<0.01),	T: 0, C1 (WM):1, C2 (Placebo): 1; AEs: T: slight erythema & irritation (2), C1: erythema & lesion enlarged (2), C2: none	SG: L AC: U BPt: U BPl: U BOA: U IOD: U SOR: L

	ext. HM + int. HM vs ext. APP + int. HM vs ext. placebo + int. HM.	2) erythema, scaling & induration: T/C1<C2 ($p<0.01$), 3) lesion area: T≈C1≈C2		
Wang, J. X., 2002; Changsha, China; 8 weeks; 1 year	T: 112/112, C: 56/56; T: 64/48, C: 30/26; T: 28-70 yrs, C: 32-68 yrs; 2 groups, active-control: ext. HM vs ext. APP.	Psoriasis vulgaris. Global PASI: T<C ($p<0.001$), Clinical efficacy: T>C ($\chi^2=6.25$, $p<0.05$), Relapse comparison: T<C ($\chi^2=5.50$, $p<0.05$)	None; AEs: NS	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Xu, J., 2009; Beijing, China; 8 weeks; 3 months	T1:31/30, T2:31/30, C:31/30; T1:21/9, T2:22/8, C:23/7; T1:37.47±11.49 yrs, T2:39.10±11.41 yrs, C:38.13±12.79 yrs; blood-heat syndrome, 3 groups: ext. HM + int. HM vs ext. HM + int. HM vs ext. placebo + int. HM.	Active psoriasis. Clinical efficacy: T1/T2>C ($p<0.05$), T1≈T2 ($p>0.05$); Reduction of modified PASI scores: T1/T2>C ($p<0.05$), Lesion area rating: T1≈T2≈C; Single symptom scores (erythema, scaling, infiltration & itching): all T1/T2<C ($p<0.05$); Single symptom time to improvement: all T1/T2<C ($p<0.05$)	T1: 1,T2: 1,C: 1; AEs: slight erythema & irritation (T1=2, T2=1, C=1)	SG: L AC: U BPt: L BPl: U BOA: U IOD: L SOR: L
Yang, Y. D., 2011; Qingdao, China; 8 weeks; NS	T: NS/96, C: NS/86; T: 51/45, C: 45/41; T: 36.5, (18-65) yrs, C: 33.5, (18-62) yrs; 2 groups, active-control: ext. HM + int. pharm. vs ext. APP + int. pharm.	Psoriasis vulgaris. Clinical efficacy based on reduction of PASI score T>C ($\chi^2=5.0$, $p<0.05$)	NS; AEs: No SAE, mild itching & burning (T=4, C=5)	SG: U AC: U BPt: H BPl: H BOA: U IOD: U SOR: L
Zhou, N., 2009; Beijing, China; 4 weeks; NS	T: 54/51, C: 54/49; T: 23/28, C: 28/21; T: (39.4±15.0) yrs, C: (41.2±13.3) yrs; 2 groups, multi-centre, placebo-controlled, RCT: ext. HM + int. HM vs ext. placebo + int. HM.	Blood-heat syndrome Psoriasis. Remarkably effective rate (RER): T>C ($\chi^2=13.0998$, $p=0.0003$); total effective rate (TER): T>C ($\chi^2=12.7298$, $p=0.0004$); PASI scores: T<C ($p<0.05$); Score of erythema, infiltration & lesion area: all T<C ($p<0.01$); Score of scaling: T≈C ($p>0.05$); Score of itching: T<C ($\chi^2=8.1145$, $p=0.0044$)	T: 3 (1 dissatisfied with efficacy, 2 various reasons), C: 5 (1 dissatisfied with efficacy, 4 various reasons); AEs: none	SG: L AC: U BPt: L BPl: U BOA: U IOD: L SOR: L
Zhu, L.,	T: 41/41, C: 44/44;	Psoriasis vulgaris.	None;	SG: U

2008; Sichuan, China; 2 weeks; NS	T: 24/17, C: 26/18; T: 39.5±11.3, (18-65) yrs, C: 41±10.5, (19-64) yrs; 2 groups, placebo-control: ext. HM vs ext. APP.	Clinical efficacy based on PASI: T≈C (χ^2=2.125, p=0.05)	AEs: T: slight tingling sensation (7), C: slight burning (6)	AC: U BPt: U BPl: U BOA: U IOD: L SOR: L

T: treatment group, C: control group, R/A: registration/analysis, M/F: male/female, NS: not stated, Pharm.: pharmaceutical treatment, ext.: external, int.: internal, yrs: years, wks: weeks, mins: minutes, RCT: randomised clinical trial

Risk of Bias Categories
SG: sequence generation, AC: allocation concealment, BPt: blinding of participants, BPl: blinding of personnel, BOA: blinding of outcome assessment, IOD: incomplete outcome data, SOR: selective outcome reporting

Risk of Bias Judgements
L: low risk, U: unclear risk, H: high risk

Table 6.4 Interventions used in the 9 studies on topical herbal formulae for treating psoriasis [adapted from Deng 2013 (158)]

Study ID	External HMs and ingredients	HM vs APP/Plac (T vs C)	Co-intervention (same in T&C)
Gao 2006	*Liubai Baibi* cream: Bai xian pi (*Dictamnus dasycarpus* Turcz., bark) 30g, Bai zhi (*Angelica dahurica* (Fisch. ex Hoffm.) Benth. & Hook.f., root) 10g, Bai ji li (*Tribulus terrestris* L., fruit) 10g, Bai fan (*Alunite*) 10g, Bai lian (*Ampelopsis japonica* (Thunb.) Makino, root) 15g, Duan mu li (*Ostrea rivularis* Gould, shell) 30g, Zi cao (*Lithospermum erythrorhizon* Sieb.et Zucc., root) 20g, Xue jie (*Daemonorops draco* Bl., fruit-resin) 3g, Mu bie zi (*Momordica cochinchinensis* (Lour.) Spreng., seed) 10g, Fang feng (*Saposhnikovia divaricata* (Turcz.) Schischk., root) 10g, Hu huang lian (*Picrorhiza scrophulariiflora* Pennell, root) 10g, Da feng zi (*Hydnocarpus anthelmintica* Pier., seed) 10g, Ku shen (*Sophora flavescens* Ait., root) 15g, Ce bei ye (*Biota orientalis* (L.) Endl., leaf) 10g, Sheng gan cao (*Glycyrrhiza uralensis* Fisch., root) 30g. Vehicle consisted of stearic acid 300 g, white petrolatum 250 g, glycerol 50 g, triethanolamine 200 ml (used in water phase) and sesame oil (used in oil phase).	T: 2 X day (30 mins before sleep, and after getting up) use enough cream to cover the lesions. C: En Fu cream (clobestasol), 2 X day.	Folic acid (10 mg): oral, 3 X day; Vitamin E (0.2 g): oral, 3 X day
Lassus 1991	*Oleum horwathiensis* spraying agent (Psoricur®): manufactured by Unifarm International, Sweden. *Achillea millefolium* L. herb, *Allium sativum* L. bulb, *Calendula officinalis* L., flower, *Taraxacum officinale* F.H Wigg, root, *Urtica dioica* L. leaf and *Veronica officinalis* L. herb, in cosmetic soft paraffin.	T: apply to affected areas with a mechanical spray pump directly from the plastic bottle package, 1 X day. C: vehicle oil (spraying agent): apply to affected areas with a mechanical spray pump directly from the plastic bottle package, 1 X day.	None
Lu 2004	*Queyin* tincture: Bai xian pi (*Dictamnus dasycarpus* Turcz., bark), Ku shen (*Sophora flavescens* Ait., root) each 30g, Huang qin (*Scutellaria baicalensis* Georgi, root) 20g, Lei gong teng (*Tripterygium wilfordii* Hook. f., root), Tu da huang (*Rheum palmatum* L., root) 30g.	T: HM in water with 75% alcohol, 1000ml, for two weeks, then filter and set aside. Lesion on the limbs/chest-back used as target area (7.5-30 cm^2), 2 X day. C: Piyanning tincture (Compound Fluocinonide	None

		Tincture): Lesion on the limbs/chest-back used as target area (7.5-30 cm2). 2 X day.	
Song 2007	T: Compound *E-Bei* ointment(CEBO): 2.5% volatile oil of E zhu (*Curcuma phaeocaulis* Valeton, rhizome), 5% aqueous extract of Wu bei zi (*Rhus chinensis* Mill., gall), prepared by the authors' hospital.	T: 2 X day, topically. C1 (WM): Daivonex ointment (Calcipotriol): manufactured by LEO Pharmaceutical Co., Ltd., Denmark. 2 X day. C2 (Placebo): Vehicle of CEBO, prepared by the authors' hospital. 2 X day.	Shaoxian Wan (0.9 g/pill): Chong lou (*Paris polyphylla* Smith, root), Bai xian pi (*Dictamnus dasycarpus* Turcz., bark), etc. in ratio of 1:1, total crude drug at 2.35g, and prepared by the authors' hospital. Oral 1 pill X 2 X day.
Wang 2002	1# Herbal Bath Formula (for blood-heat syndrome): Sheng da huang (*Rheum palmatum* L., root) 100g, Huang bai (*Phellodendron amurense* Rupr., bark) 100g, Ku shen (*Sophora flavescens* Ait., root) 100g, Hu zhang (*Polygonum cuspidatum* Sieb. et Zucc., root) 100g, Ye ju hua (*Chrysanthemum indicum* L., flower) 60g, She chuang zi (*Cnidium monnieri* (L.) Cusson, seed) 60g, Pu gong ying (*Taraxacum mongolicum* Hand.-Mazz., herb) 60g, Bai zhi (*Angelica dahurica* (Fisch. ex Hoffm.) Benth. & Hook.f. , root) 60g, Qian li guang (*Senecio scandens* Buch.-Ham. aerial parts) 60g, Shi chang pu (*Acorus tatarinowii* Schott., root) 30g, Hong hua (*Carthamus tinctorius* L., flower) 30g, Bo he (*Mentha haplocalyx* Briq., leaf) 30g, Pi xiao (*Mirabilite*) 30g, Ku fan (*Alumen*) 30g. 2# Herbal Bath Formula (for blood-deficiency syndrome): Da sheng di (*Rehmannia glutinosa* (Gaertn.) Libosch., root) 100g, Quan dang gui (*Angelica sinensis* (Oliv.) Diels, root) 100g, Ji xue teng (*Spatholobus suberectus* Dunn., stem) 100g, Ci wu jia pi (*Acanthopanax senticosus* (Rupr. et Maxim.) Harms., bark) 60g, Di gu pi (*Lycium barbarum* L., root) 60g, Qi ye yi zhi hua (*Paris polyphylla* Smith, root) 60g, Xu chang qing (*Cynanchum paniculatum* (Bge.) Kitag., root) 60g, Ci ji li (*Tribulus terrestris* L., fruit) 60g, Hang bai ju (*Chrysanthemum morifolium* Ramat., flower) 60g, Wei ling xian (*Clematis hexapetala* Pall., root) 60g, Chu tao ye (*Broussonetia papyrifera* (L.) Vent., fruit) 60g, Ce bai ye (*Biota orientalis* (L.) Endl., leaf) 60g, Dan shen (*Salvia miltiorrhiza* Bge., root)	T: 1#/2#: in 180-200L water boiled for 20 mins, then filter into warm liquid for bath, 20 mins, 2 X day. C: 0.1% anthralin ointment 2 X day (in the morning and at night).	None

	60g, Hua jiao (*Zanthoxylum bungeanum* Maxim., seed) 30g.		
Xu 2009	T1: Conventional *Qinbai Ruangao* (ointment): 10% Huang qin (*Scutellaria baicalensis* Georgi, root) and 10% Huang bai (*Phellodendron amurense* Rupr., bark), prepared by the authors' hospital. T2: Fine *Qinbai Ruangao* (ointment): same ingredients as the above (finely ground), prepared by the authors' hospital and Tsinghua University.	T1/T2: clean affected skin, then apply the ointment, 2 X day. C: white vaseline ointment: provided by Hebei Lanlian Feitian Petro Chemical Co., Ltd. Clean the affected skin, then apply the ointment, 2 X day.	*Liangxue Huoxue Tang* (decoction): Huai hua (*Sophora japonica* L., flower), Zi cao gen (*Lithospermum erythrorhizon* Sieb. et Zucc., root), Chi shao (*Paeonia veitchii* Lynch, root), Bai mao gen (*Imperata cylindrica* Beauv.var.major (Nees) C.E., stem), Sheng di (*Rehmannia glutinosa* (Gaertn.) Libosch., root), Dan shen (*Salvia miltiorrhiza* Bge., root), Ji xue teng (*Spatholobus suberectus* Dunn., stem), etc. in 400ml decoction, prepared by the authors' hospital, oral, 2 X day.
Yang 2011	*Liubaibaibi* cataplasm: Sheng gan cao (*Glycyrrhiza uralensis* Fisch. root), Bai xian pi (*Dictamnus dasycarpus* Turcz., bark), Bai ji li (*Tribulus terrestris* L., fruit), Bai Lian (*Ampelopsis japonica* (Thunb.) Makino root), Zi cao (*Lithospermum erythrorhizon* Sieb. et Zucc., root), Hu huang lian (*Picrorhiza scrophulariiflora* Pennell, root), Ku shen (*Sophora flavescens* Ait., root), Ce bai ye (*Biota orientalis* (L.) Endl., leaf), Bai zhi (*Angelica dahurica* (Fisch.ex Hoffm.) Benth.& Hook.f., root), Bai fan (Alunite), Sheng mu li (*Ostrea rivularis* Gould, shell), Fang feng (*Saposhnikovia divaricata* (Turcz.) Schischk., root), Da feng zi (*Hydnocarpus anthelmintica* Pier., seed), and Mu bie zi (*Momordica cochinchinensis* (Lour.) Spreng., seed).	T: apply enough cataplasm to cover the lesions for 6 hours, 2 X day (morning & evening). C: En Fu cream (clobestasol), 2 X day.	Folic acid (10 mg): oral, 3 X day; Vitamin E (0.2 g): oral, 3 X day
Zhou 2009	New *Pulian* Ointment: Huang qin (*Scutellaria baicalensis* Georgi, root), Huang bai (*Phellodendron amurense* Rupr., bark), Qing dai (*Indigo naturalis,* namely dried powder manufactured from: *Baphicacanthus cusia* (Nees) Brem., *Indigofera tinctoria* L., *Isatis tinctoria* L., *Isatis indigotica* Fort., or *Polygonum tinctorium* Ait.), Zi cao (*Lithospermum erythrorhizon* Sieb. et Zucc., root), Bing pian (*borneol*), water phase (lauryl sulfonate), and oil phase (sesame oil, glycerine monostearate, tween-80, and ethyl hydroxy benzoate) prepared by the authors' hospital.	T: 2 X day, topically. C: placebo ointment: mainly contained Jian qu (Massa Fermentata Medicinalis) prepared by the same hospital. 2 X day.	conventional clearing heat & cooling blood decoction: mainly consisted of Pu gong ying (*Taraxacum mongolicum* Hand.-Mazz., herb) 10g, Lian qiao (*Forsythia suspensa* (Thunb.) Vahl, fruit) 12g, Ban lan gen (*Isatis tinctoria* L., root) 30g, Da qing ye (*Isatis indigotica* Fortune, leaf) 15g, Bai mao gen (*Imperata cylindrica* Beauv. var. major (Nees) C.E., stem) 30g, Jin yin hua (*Lonicera*

			japonica Thunb., flower) 15g, Xia ku cao (*Prunella vulgaris* L., herb) 15g, Mu dan pi (*Paeonia suffruticosa* Andr., bark) 15g, Chi shao (*Paeonia veitchii* Lynch, root) 15g, Bai shao (*Paeonia lactiflora* Pall. , root) 15g, Sheng di (*Rehmannia glutinosa* (Gaertn.) Libosch., root) 15g, Xuan shen (*Scrophularia ningpoensis* Hemsl., root) 15g. 1 X day, which was decocted to divide into 2 parts for twice (in the morning and evening) oral application with swallowing 0.3g powder of Ling yang jiao (*Saiga tatarica* L., horn).
Zhu 2008	*Xiaoxuanling* formula: mainly contained Wu bei zi (*Rhus chinensis* Mill., gall), Yang shu ye (*Populus simonii* Carr., leaf), Shou wu (*Polygonum multiflorum* Thunb., root), Zhi liu huang (sulphur), Di fu zi (*Kochia scoparia* (L.), fruit), which was prepared by the authors' hospital.	T: 2 X day, topically. C: tretinoin cream (0.025% Diwei cream- Vitamin A acid cream): manufactured by Chongqing Huapont Pharm. Co., Ltd., 2 X day.	None

T: treatment group, C: control group, HM: herbal medicine, APP: anti-psoriatic pharmacotherapy

6.2.3.1 Description of studies

Oleum horwathiensis formula (1 RCT)

Lassus and Forsström have conducted a double-blind placebo-controlled study involving 50 patients with mild to moderate psoriasis vulgaris. They revealed that a multi-herb proprietary medicine called *Oleum horwathiensis* sprayed on psoriatic lesions produced a marked decrease in symptom severity after 12 weeks (226). The placebo group also experienced some improvements; these were less pronounced than those in the treatment group. However, no significance tests were performed. The tolerability and cosmetic acceptance of *Oleum horwathiensis* was found to be good; this preparation was effective on scalp lesions.

Herbal bath formula (1 RCT)

Wang *et al.* compared the effect of No. 1 and No. 2 herbal bath formula with that of the 0.1% anthralin ointment (n = 56) in the treatment of psoriasis vulgaris (229). Participants in 'blood-heat' syndrome and 'blood-deficiency' syndrome groups (n = 112 for both groups) were administered No. 1 formula and No. 2 formula, respectively. The outcomes were PASI score, clinical efficacy and relapse proportion. Data for the 2 herbal bath formulae were pooled. The authors reported significant differences between clinical efficacy and a relapse rate in the HM and anthralin groups after 8 weeks of treatment.

Queyin formula (1 RCT)

Lu and Miao compared the effect of a compound HM called Queyin tincture (n = 31) with that of a steroid agent, Piyanning tincture, (n = 22) on randomly selected target lesions (7.5–30 cm^2) (227). The overall clinical efficacy was evaluated on the basis of changes in PASI scores. After 18 days of treatment, there was a significant difference between the 2 groups. Queyin tincture was considered to have satisfactory efficacy for external use in cases of psoriasis.

Liubai Baibi formula (2 RCTs)

The study of Gao *et al.* evaluated the efficacy of a compound HM called Liubai Baibi,

administered in a cream form (n = 192), in comparison with that of clobestasol (En Fu cream) (n = 184). Both the groups also received oral folic acid and vitamin E (225). The overall clinical efficacy was assessed after 8 weeks on the basis of PASI score change. There was a significant difference between the 2 groups without any serious AEs (SAEs) in either group. Therefore, Liubai Baibi cream was considered to be safe for the treatment for psoriasis vulgaris.

A comparison between the efficacy of the Liubai Baibi cataplasm (n = 96) and clobestasol (En Fu cream) (n = 86), with oral folic acid and vitamin E as co-interventions, was the subject of another RCT. The trial lasted for 8 weeks (231). The cataplasm contained similar ingredients to those in the cream (225, 231). A significant reduction in the PASI score was found for the cataplasm. No SAEs were reported in either group. Moreover, the cataplasm group had fewer cases of slight skin irritation than the clobestasol group. The authors concluded that the Liubai Baibi cataplasm was safe and effective and recommended its application in treating psoriasis vulgaris.

Compound E-Bei (1 RCT)

Song *et al.* compared the E-Bei ointment (n = 60) with the calcipotriol ointment (n = 30) and placebo, which was the vehicle for the herbal ointment (n = 30). The trial lasted for 4 weeks with follow-ups at 3 and 9 months (228). All the 3 groups were also given the same herbal pill (Shaoxian Wan). The outcome measures were modified PASI, individual symptom scores (erythaema, scaling, induration, itching and lesion area) and overall therapeutic effectiveness. In comparison with the vehicle ointment group, modified PASI and individual symptom scores improved in both the E-Bei ointment and calcipotriol ointment groups, but not in lesion area. Calcipotriol and placebo groups had 1 dropout each. There were 2 cases of rash and irritation in the E-Bei ointment group. Slight rash and lesion expansion were noted in 2 cases in the calcipotriol group; these cleared within 10 days. There were no AEs in the placebo group. The authors concluded that the E-Bei ointment was not inferior to the calcipotriol ointment. The herbal ointment reduced itching more rapidly than calcipotriol.

Xiaoxuanling formula (1 RCT)

An RCT by Zhu *et al.* compared the Xiaoxuanling topical formula (made by the hospital) with routine therapy of Tretinoin cream (0.025% Vitamin A acid cream) as treatment for

psoriasis vulgaris. The measured outcome was overall clinical efficacy based on the PASI score change (233). The trial lasted for 2 weeks. No differences were observed between overall clinical efficacies or AE incidences. The authors suggested that Xiaoxuanling was a good clinical option for treating psoriasis; it caused no SAEs and was cheaper than the conventional cream.

Compound Qinbai formula (1 RCT)

In a participant-blinded 8-week RCT, Xu *et al.* compared 2 forms of the same herbal ointment with a petroleum jelly. There were 3 experimental groups (n = 31 in each) (230). The study enrolled 93 participants, and there was 1 dropout in each group. The herbal ointments compared were 'conventional' Qinbai ointment (n = 30) and 'fine' Qinbai ointment (finely ground to improve the release of constituents) (n = 30). The placebo group was treated with petroleum jelly (n = 30). All the patients had been diagnosed according to TCM principles as belonging to the 'blood-heat' type. All the participants also received the same herbal decoction, administered orally (Liangxue Huoxue Tang). The outcome measures, obtained at 2, 4, 6 and 8 weeks, were modified PASI and individual symptom scores (erythaema, scaling, induration, itching and lesion area). After 8 weeks, all 3 groups demonstrated significant improvements in overall modified PASI scores and lesion area in comparison with baseline. For both types of ointments, the improvements were greater than those for the petroleum jelly alone. In comparison with the control group, the 2 herbal ointment groups showed improvements in the individual symptom scores for scaling, induration and itching but not in erythaema. However, these differences were not statistically significant. The authors concluded that the herbal ointments were more effective than the petroleum jelly and that the fine Qinbai ointment was faster-acting than the conventional ointment.

New Pulian formula (1 RCT)

A single-blind RCT was conducted by Zhou *et al.* to examine the efficacy of New Pulian Ointment in comparison with that of the placebo ointment. The trial involved 108 patients with psoriasis vulgaris of the 'blood-heat' type and lasted for 4 weeks (232). The ointment was a modification of Pulian Ointment, made up in a less sticky vehicle than the conventional type to make it more acceptable to patients. The participants also received an oral HM decoction for 'clearing heat and cooling blood' and a number of foods were

forbidden. Outcome measures were (a) PASI scores and skin lesion symptoms (scaling, erythaema, infiltration and lesion area), (b) itching score and (c) AEs and safety. After 4 weeks, significant differences were observed between the 2 groups for all the above mentioned measures, except the scaling score, without any AEs. The researchers concluded that the new ointment was safe, improved treatment efficacy and could be regarded as reliably effective for the 'blood-heat' syndrome of psoriasis.

6.2.3.2 Methodological assessment

Risk of bias evaluations are listed in Table 6.3 (171). The authors of all trials either stated that their studies had been 'randomised' or used a similar expression. Three studies stated the method of random sequence generation: 'sealed envelopes' (228), 'random number table' (230) and 'randomising digital table' (232); therefore, they were judged as having 'low' risk of bias in this category. No study provided information on the method of allocation concealment; therefore, they were all judged as having 'unclear' risk of bias for this item. Three placebo-controlled studies applied identical vehicle preparations and were blinded to participants and were considered have 'low' risk of bias in this category (226, 230, 232). In the category of blinding of participants, 2 studies were judged as having 'high' risk of bias because different interventions were applied in different groups; therefore, unblinding appeared likely (229, 231). The same 2 studies were also judged as having high risk of bias in personnel blinding (229, 231). One study was blinded to personnel and judged as having 'low' risk of bias in this category (226). All the studies were judged as having 'unclear' risk of bias in blinding of outcome assessment because none provided the relevant information. Gao *et al.* (2006) and Yang *et al.* (2011) did not provide the number of enrolled participants (225, 231). Song *et al.* (2007) did not provide reasons for dropouts (228). These 3 studies were judged to have 'unclear' risk of bias for incomplete outcome data. The remaining studies reported that all the patients completed the study; these studies were judged as having 'low' risk of bias for this category. All studies reported all outcomes; therefore, bias due to selective reporting was judged as low.

6.2.3.3 Meta-analysis

Numerical outcome data suitable for meta-analysis in RevMan 5.1 were reported by eight studies (Table 6.5) ; 1 study did not provide suitable data (226). Outcome measures included overall clinical efficacy (n = 8) (225, 227-233), symptom score on scaling, erythaema,

induration, itching and lesion area (n = 2) (228, 230), PASI score (n = 2) (229, 232) and modified PASI score (n = 2) (228, 230).

Table 6.5 Distribution of RCTs suitable to *meta-analysis* with RevMan 5.1 by outcome measure and study design [adapted from Deng 2013 (158)]

Study design / **Outcome measures**	**ext. HM** **vs** **ext. APP**	**ext. HM + int. HM** **vs** **ext. APP + int. HM**	**ext. HM + int. pharm.** **vs** **ext. APP + int. pharm.**	**ext. HM + int. HM** **vs** **ext. placebo + int. HM**
Clinical efficacy	Lu 2004, Wang 2002, Zhu 2008	Song 2007	Yang 2011, Gao 2006	Song 2007, Xu 2009, Zhou 2009
Scaling score	X	Song 2007	X	Song 2007, Xu 2009
Erythaema score	X	Song 2007	X	Song 2007, Xu 2009
Induration score	X	Song 2007	X	Song 2007, Xu 2009
Itching score	X	Song 2007	X	Song 2007,

				Xu 2009
Lesion area	X	Song 2007	X	Song 2007, Xu 2009
PASI	Wang 2002	X	X	Zhou 2009
Modified PASI	X	Song 2007	X	Song 2007, Xu 2009

HM: herbal medicine, APP: anti-psoriatic pharmacotherapy, Pharm.: pharmaceutical treatment, ext.: external treatment, int.: internal treatment, PASI: Psoriasis Area Severity Index

Clinical efficacy

Different studies used different systems for classifying clinical efficacy and PASI reduction. Therefore, our clinical efficacy assessment only included cases with an efficacy rate of 50% or above or PASI reduction of 50% or more (185). Results were analysed using RR and random-effect model. In meta-analyses, a higher score reflects greater efficacy.

Of the 8 studies that provided data suitable for meta-analysis, 4 compared topical HM with placebo and all used an oral Chinese medicine in both groups (230, 232, 235). Three studies tested external HM versus external APP (227, 229, 233), 1 used an additional internal HM in both groups (228) and 2 administered internal pharmaceuticals in both groups (225, 231). The meta-analysis used pooled data for 4 subgroups of studies, described below.

Group 1. External HM + internal CM vs. external placebo + internal CM (3 studies, 7 groups)

For the study by Song *et al.* (2007), the comparison between the E-Bei ointment and placebo failed to reach statistical significance (RR 7.38, 95% CI: 0.44–124.90). Similarly, the differences observed between conventional and fine Qinbai ointments and placebo in the study by Xu *et al.* (2009) were not significant: conventional Qinbai ointment (RR 1.21, 95% CI: 1.00–1.46); fine Qinbai ointment (RR 1.17, 95% CI: 0.95–1.43). The comparison between New Pulian Ointment and placebo revealed significant differences in the favour of HM (RR 3.68, 95% CI: 1.64–8.27) (232). For the pooled data, a significant difference was found in the favour of HM (RR 1.40, 95% CI: 1.01–1.94, p = 0.04); however, analysis revealed high heterogeneity (66%) (Fig.6.4). Sensitivity analysis showed that the high heterogeneity was caused by the use of PASI score as the basis of efficacy evaluation (232), whereas the other trial used modified PASI. Although there was a tendency to favour HMs, meta-analyses revealed no differences between HMs and their respective placebos in the studies by Song *et al.* (2007) and Xu *et al.* (2009). Our results did not support the original conclusions that these ointments were superior to placebo for this outcome. However, the results of meta-analysis were in agreement with conclusions of the study by Zhou *et al.* (2009).

Group 2. External HM vs. external APP (3 studies, 6 groups)

For the studies testing HM versus APP, there was a significantly higher efficacy rate for Queyin tincture than for Fluocinonide tincture (RR 1.42; 95% CI: 1.01–1.99) and for No. 1 and No. 2 Herbal Bath formulae than for the 0.1% anthralin ointment (RR 1.29; 95% CI: 1.03–1.61). No significant difference was found between efficacies of Xiaoxuanling and Tretinoin cream (RR 1.07; 95% CI: 0.38–3.06). These results were consistent with the conclusions of the study. For the pooled data, a significant difference between external HM and external APP was found (RR 1.32, 95% CI: 1.10–1.58, p = 0.003) (Fig. 6. 4).

Group 3. External HM + internal CM vs. external APP + internal CM (1 study, 2 groups)

No significant difference between the E-Bei ointment and calcipotriol control was found in the study of Song *et al.* (228) (RR 1.69, 95% CI: 0.37–7.64) (228) (Fig. 6.4). This supported the authors' conclusion that the efficacy of HM was not inferior to that of calcipotriol.

Group 4. External HM + internal WM vs. external APP + internal WM (2 studies, 4 groups)

The 2 Liubai Baibi preparations showed better efficacy than external clobestasol (with oral folic acid plus vitamin E as co-intervention). The results for Liubai Baibi cream were RR 1.39; 95% CI: 1.24–1.55 (225) and those for cataplasm were RR 1.29; 95% CI: 1.07–1.55 (231). The pooled data revealed a significant difference in the favour of external HM (RR 1.36; 95% CI: 1.23–1.50, p < 0.00001) with zero heterogeneity (Fig. 6.4). This result supported the conclusions of the study.

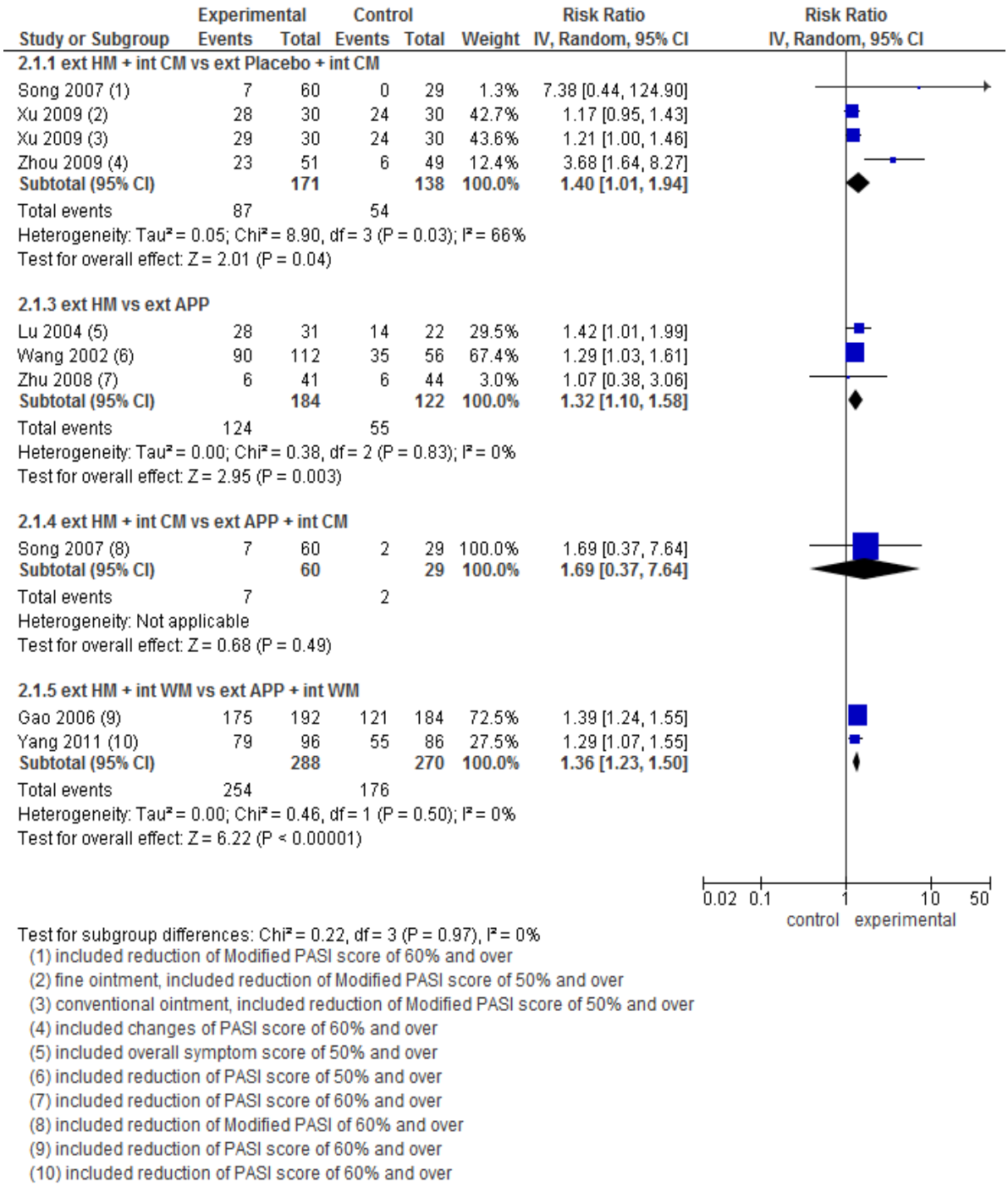


Fig. 6.4 Forest plot of clinical efficacy: external herbal medicine (HM) versus external placebo/anti-psoriatic pharmacotherapy (APP) with or without co-interventions of internal herbal medicine (int HM) or internal Western medicine (int WM) used in both groups [adapted from Deng 2013 (158)]

Symptom scores

Symptom scores were presented as outcome measures in 3 studies (228, 230, 232). The studies used a internal HM in both experimental arms. However, the symptom scores given in Zhou *et al.* (2009) were difference scores and were not suitable for RevMan 5.1. analysis.

Scaling (2 studies, 6 groups)

A significant difference in the efficacy of the E-Bei ointment in comparison with that of placebo was found in the study by Song *et al.* (2007) (SMD −1.20, 95% CI: −1.68 to −0.72). However, the differences between HM and calcipotriol in the other arm of the study failed to reach significance (SMD 0.17, 95% CI: −0.27 to 0.62). In the study by Xu *et al.* (2009), there were significant differences between the effects of both fine and conventional Qinbai ointments and placebo (each SMD −0.53, 95% CI: −1.05 to −0.02), in the favour of HMs. Analysis of pooled data showed significant differences between the effects of external HMs and external placebos (SMD −0.77, 95% CI: −1.21 to −0.32) in the treatment of scaling.

Erythaema (2 studies, 6 groups)

In the study of Song *et al.* (2007), a significant difference was observed between the effect of the E-Bei ointment and placebo (SMD −0.88, 95% CI: −1.34 to −0.42); however, there were no significant differences in comparison with calcipotriol (SMD 0.38, 95% CI: −0.07 to 0.83). Xu *et al.* (2009) did not demonstrate significant differences between the fine (SMD −0.20, 95% CI: −0.71 to 0.31) or conventional Qinbai ointment (SMD −0.09, 95% CI: −0.60 to 0.42) and placebo. Pooled data analysis did not reveal differences between the effects of external HM and external placebo (SMD −0.40, 95% CI: −0.90 to 0.10, p = 0.12) on erythaema.

Induration (2 studies, 6 groups)

The comparison of the E-Bei ointment and placebo in a study by Song *et al.* (228) revealed a significant difference between efficacies (SMD −0.99, 95% CI: −1.45 to −0.52) but no difference in comparison with calcipotriol (SMD 0.33, 95% CI: −0.12 to 0.77). Xu *et al.* (2009) found no differences between the fine (SMD −0.61, 95% CI: −1.13 to −0.09) or conventional Qinbai ointment (SMD −0.54, 95% CI: −1.06 to −0.03) and placebo. The pooled data showed a significant difference between the effect of external HM and external placebo (SMD −0.73, 95% CI: −1.02 to −0.44) in the treatment of induration.

Itching (2 studies, 6 groups)

Song *et al.* (2007) have reported a significant difference between the effect of the *E-Bei* ointment in comparison with that of placebo (SMD −0.88, 95% CI: −1.34 to −0.41) but no

difference in comparison with the effect of calcipotriol (SMD −0.04, 95% CI: −0.48 to 0.40). In the study of Xu *et al.* (2009), there were differences between fine (SMD −0.62, 95% CI: −1.14 to −0.10) and conventional Qinbai ointments (SMD −0.54, 95% CI: −1.06 to −0.03) and placebo. The pooled data revealed a significant difference between the effect of external HM and external placebo (SMD −0.69, 95% CI: −0.98 to −0.41) on itching.

Lesion area (2 studies, 6 groups)

No significant differences were found in comparison of the E-Bei ointment with the calcipotriol ointment or placebo or in the comparison between fine and conventional Qinbai ointments with placebo. Therefore, there was no difference between the effect of HM and placebo in pooled result analysis (SMD −0.11, 95% CI: −0.39 to 0.17, p = 0.45).

PASI score and modified PASI score

PASI is used as a standard measure of psoriatic severity in terms of erythaema, induration and scaling (236). Currently modified versions of PASI are also used in clinical practice and research. The modified PASI used by Song *et al.* (2007) and Xu *et al.* (2009) adds a score for itching and follows the national guideline on Chinese Herbal Medicine trials (111). Another 2 studies used classical PASI scores (229, 232).

PASI score (2 studies, 4 groups)

Zhou *et al.* (2009) found that New Pulian Ointment was superior to external placebo when used with the same oral HM as co-intervention. This was confirmed (SMD −0.41, 95% CI: −0.80, −0.01). Wang *et al.* (2002) reported that the 2 herbal bath formulae were more effective than the anthralin ointment, and this result was also confirmed (SMD −0.97, 95% CI: −1.31, −0.63).

Modified PASI score (3 studies, 7 groups)

Both fine (SMD: −0.79, 95% CI: −1.32 to −0.27) and conventional (SMD: −0.70, 95% CI: −1.22 to −0.18) forms of the Qinbai ointment resulted in significant improvements in comparison with placebo in the study by Xu *et al.* (2009). Song *et al.* (228) reported that in comparison with placebo, the E-Bei ointment showed a significant effect (SMD: −0.87, 95%

CI: −1.33 to −0.41). Pooled data showed a significant difference between this external HM and external placebo (SMD: −0.79, 95% CI: −1.08 to −0.51).

Song *et al*. (2007) also compared the effect of the E-Bei ointment and calcipotriol and found no difference (SMD: 0.15, 95% CI: −0.29 to 0.60, p = 0.50), which suggested similar reductions in modified PASI scores for the 2 remedies.

6.2.3.4 AEs

AE information was supplied by 7 studies, and 2 studies did not provide any information (227, 229). Among the 7 studies, 1 reported no adverse effects (232). Of the 6 remaining studies, 2 stated that there were no SAEs (225, 231).

Symptoms of local irritation were found in all the studies reporting AEs. Slight erythaema and irritation, slight tingling sensation and mild itching and burning were the most frequent events. There were 24 AE cases among the 519 participants in the assessable treatment groups, (4.62% incidence) and no SAEs were reported.

6.2.3.5 Principal herbs used in the studies

Among the examined medications, 54 different herbs were externally applied, 8 of which were also used in co-interventions as oral herbal decoctions (2 studies) or pills (1 study). Another 11 herbs were exclusively used in co-interventions. The herb most commonly used in the external herbal formulae was Ku shen (*Sophora flavescens* Ait., root) (4 studies). Seven herbs were used in 3 studies each: Zi cao (*Lithospermum erythrorhizon* Sieb.et Zucc., root), Bai xian pi (*Dictamnus dasycarpus* Turcz., bark), Bai zhi [*Angelica dahurica* (Fisch.ex Hoffm.) Benth.& Hook.f., root], Bai ji li (*Tribulus terrestris* L., fruit), Ce bei ye [*Biota orientalis* (L.) Endl., leaf], Huang qin (*Scutellaria baicalensis* Georgi, root) and Huang bai (*Phellodendron amurense* Rupr., bark). Eleven herbs were used twice and 35 were used once.

Two studies, Gao *et al.* (2006) and Yang *et al.* (2011), used very similar topical formulae, with 14 herbs in common. Both the formulae were more effective than the tested APP. Formulae that had several herbs in common with those used by those 2 studies were used by Lu & Miao (2004) and Wang *et al.* (2002). Ku shen was used in all 4 studies. Herbal preparations of Bai xian pi, Bai zhi, Bai ji li and Ce bei ye were each included in 3 of these

studies. Because all the 4 studies analysed comparisons with APP, the data for these studies were pooled. Analysis showed a greater clinical efficacy for HM groups than APP groups (RR 1.35, 95% CI: 1.24–1.47). The studies of Xu *et al.* (2009) and Zhou *et al.* (2009) had 2 herbs in common: Huang qin and Huang bai. Both studies compared HM with placebo; therefore, the data could be pooled. However, the results were conflicting (RR 1.36, 95% CI: 0.99–1.87) (Fig. 6.5).

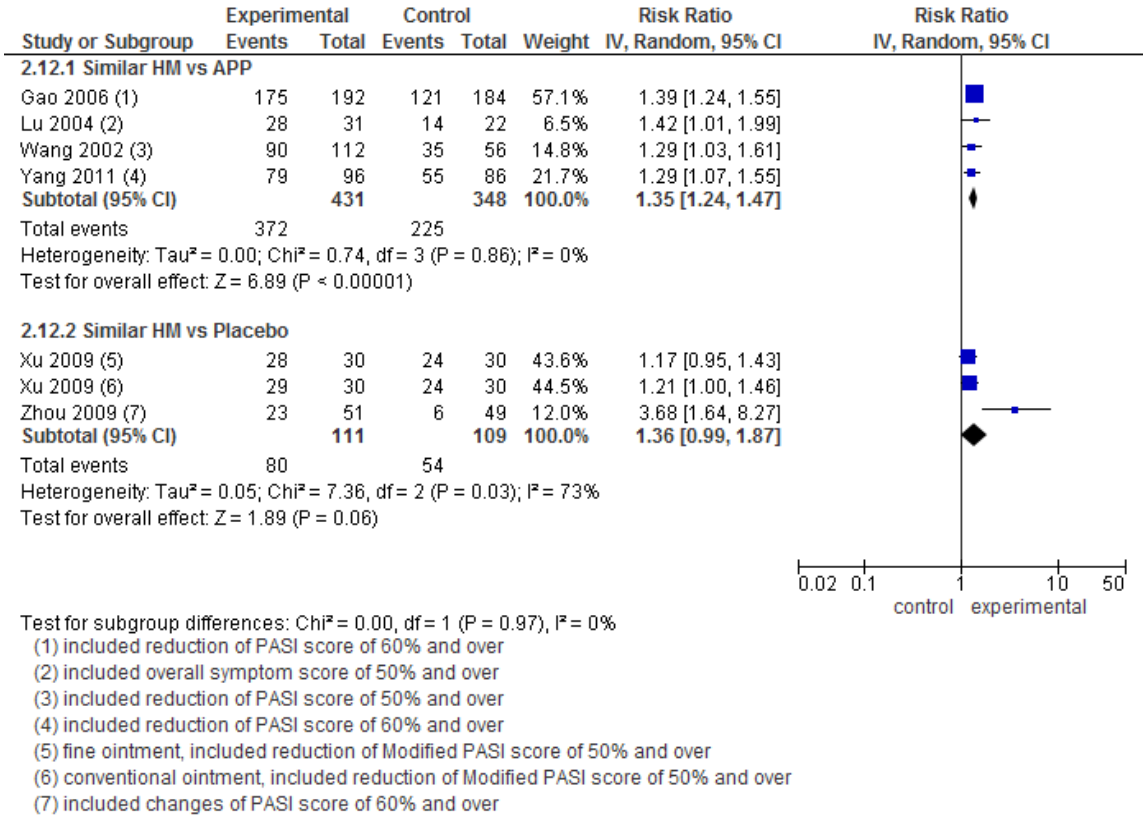


Fig. 6.5 Forest plot of clinical efficacy of trials using formulae with similar herbal ingredients: herbal medicine (HM) versus anti-psoriatic pharmacotherapy (APP) or HM versus placebo (with co-interventions used in both groups) [adapted from Deng 2013 (158)]

To explore the possible effects of the individual HMs used in multiple studies, evidence derived from experimental studies of the effect of *S. flavescens* (source of Ku shen) and *L. erythrorhizon* (source of Zi cao) in the treatment of psoriasis will be further investigated in the next chapter.

6.2.4 Discussion

Methodological reporting weaknesses were found in all the examined studies. Only 3 studies

provided the method of sequence generation and none described allocation concealment. Three studies were blinded to participants, and 1 described blinded outcome assessment. Overall, the best quality trials were those of Lassus and Forsstrom (1991), Xu *et al.* (2009) and Zhou *et al.* (2009), closely followed by the study of Song *et al.* (2007). Unfortunately, the data supplied by Lassus and Forsstrom were not suitable for meta-analysis.

Meta-analysis of pooled data showed that topical herbal formulae improved the overall clinical efficacy (defined as an improvement of 50% or more). This improvement was demonstrated in comparisons with external placebo plus oral HM co-intervention, external APP alone and topical APP plus pharmaceutical co-intervention.

External HMs were more effective than placebo (plus oral CM co-intervention) in controlling scaling, induration and itching but not for erythaema or the lesion area. No difference between the efficacy of HMs and APP (with oral HM as co-intervention) was observed for any of these symptoms; however, these results were obtained from only 1 study. External HMs clearly improved the modified PASI score in comparison with placebo (with oral HM as co-intervention). Only single studies evaluated changes in the PASI score and compared the effect of HM and APP.

External HM interventions caused few AEs (<5%). In general, these were local effects such as slight erythaema and irritation, slight tingling sensation, and others. Therefore, these herbal remedies can be safely used in the treatment of psoriasis, at least in the short-term.

One external HM was used in 2 studies, in different forms. The results were consistent; however, these studies had some methodological issues (225, 231). Similar HMs were used in 4 studies that reported that the herbal remedies performed better than external APPs. Unfortunately, the quality of reporting in these studies was rather low. Trials by Xu *et al.* (2009) and Zhou *et al.* (2009) had 2 herbs in common, and the study quality was superior to that of the other studies. Zhou reported superior efficacy for HM in comparison with placebo. However, the severity of psoriasis was moderate at baseline (mean PASI 12.94), and the mean PASI in the treatment group fell to 5.71 (56% reduction over 4 weeks). Becayse there was no follow-up, it is unclear whether this decline could be sustained and caused by oral HM co-intervention. Consequently, it is difficult to know how much of the change could be attributed to the tested ointment. In contrast, Xu *et al.* (2009) showed no differences between experimental groups; all groups showed improvement. The main difference between

formulae used in the 2 studies was the addition of *Zi cao* (*L. erythrorhizon* root) by Zhou *et al*. Interestingly, *L. erythrorhizon* root was used as the oral HM co-intervention in the trial of Xu *et al.* (230); thus, patients in both the test and control groups were receiving this preparation. Therefore, *L. erythrorhizon* root was actually used in 4 studies in total: topically in studies of Gao *et al.* (2006), Yang *et al.* (2011) and Zhou *et al*. (2009) and orally in the study of Xu *et al.* (2009).

Because it is difficult to enrol Chinese patients in trials using placebos, many studies compare the effects of additional experimental intervention with the results of already established treatment. In case of psoriasis, this established treatment typically takes the form of systemic therapy. None of the Chinese studies evaluated here included a group that received placebo alone. Although comparisons between treatments may be informative from the clinical point of view, it is difficult to arrive at firm conclusions when co-interventions are being used.

The results may be affected by multiple factors. Nevertheless, a list of individual HMs with the best evidence of efficacy can be prepared by taking into account the combination of the results for clinical efficacy, quality of the studies and herbs that appeared in multiple trials. These HMs are Ku shen (*Sophora flavescens* root), followed by Zi cao (*L. erythrorhizon* root) and, with lesser support, Bai xian pi (*D. dasycarpus* bark), Bai zhi (*A. dahurica* root), Bai ji li (*T. terrestris* fruit) and Ce bei ye (*B. orientalis* leaf).

The methodological issues identified in the clinical trials examined here increase the risk of bias in the reported results. The relatively small sample sizes in some of the studies and lack of independent confirmation studies using the same test and control interventions also represent serious limitations. All these factors affect the reliability of results. Validity of meta-analyses using the data pooled from different studies is limited by variability in test and control interventions and different methods used to measure outcomes. Nevertheless, there is greater similarity between the interventions assessed here than the formula names suggest. Moreover, relatively recent experimental evidence indicates that at least some of these herbs have pharmacological activity relevant to psoriasis management. Certain combinations of herbs tend to recur in different preparations, suggesting the possibility of synergistic effects (208). Importantly, the caveats on over-interpretation of the evidence from the clinical studies should not be ignored. However, analysis of such studies can assist in identifying directions for more rigorous clinical and experimental research endeavours.

6.2.5 Summary

We performed a systematic review and meta-analysis of external herbal formulae for the treatment of psoriasis tested in 9 different clinical trials. Our results confirmed some potential improvements that these preparations could bring to existing psoriasis therapies. All the herbal interventions appeared relatively safe. Unfortunately, these clinical trials showed methodological weaknesses, which limit the validity of the results. However, experimental studies of the pharmacological activity of 2 main herbs used in the external herbal formulae, Ku shen (*S. flavescens* root) and Zi cao (*L. erythrorhizon* root), revealed that these herbs have anti-inflammatory, anti-proliferative, anti-angiogenic and tissue repair properties, which explain their apparent benefits in treating psoriasis.

6.3 Results for systematic review 4: External herbal medicines combined with pharmacotherapy for psoriasis: A systematic review with meta-analysis of RCTs

6.3.1 Introduction

Considerable advances have been made in the conventional management of psoriasis in recent years; however, some patients do not respond well to therapy and long-term management remains difficult (237). In Europe, 43% of psoriasis patients use some form of CAM, often in combination with conventional APP (36). In some Asian countries, herbal medicines (HMs) are commonly used. Dermatologists may advise patients to use them together with APP. This strategy may enhance the therapeutic effects and/or reduce the dosage of APP (52). The clinical efficacy and safety of externally applied HMs used in combination with APP were examined in this systematic review.

6.3.2 Method

To find the relevant publications, we searched the following databases: EMBASE, PubMed, Cochrane Library, CNKI Database and CQVIP (up to September 2012), with no limits on THE language or year. Search terms belonged to the following groups: clinical condition (psoriasis and others); intervention (herbal medicine and others) and study type (controlled trial and others), with adjustments for different databases (see Chapter 4 for lists of terms). We also searched reference lists in review articles. For Cochrane Library, because the focus is on clinical trials and systematic reviews, only the terms for clinical condition and

intervention were used.

The systematic review included RCTs using externally applied HM combined with APP (used internally and/or externally) in English, Chinese or Japanese. APPs could include emollients, corticosteroids, vitamin D3 analogues, tazarotene, coal tar, dithranol, methotrexate (MTX), ciclosporin, retinoids, fumarates and/or biologicals. Ultraviolet radiation therapy was excluded. HM was defined as any remedy consisting of natural products of plant, animal or mineral origin used singly or in combination, in any form, including oils and extracts. Vitamin and/or mineral therapies, Dead Sea cure, homeopathy, fish and animal oils were not included. Studies of multi-ingredient HMs, including vitamins and mineral and/or animal oils, were taken into account. Evaluations of psychological interventions, stress management techniques or manual therapies were not included.

Two researchers, SD and BHM, conducted the searches and extracted the characteristics of each study. The information collected included location, duration, design, participants, interventions, outcome measures, dropouts, AEs and assessed risk of bias. Any disagreements were resolved by discussions with a third researcher ALZ if agreement could not be reached. A flowchart for the process of study selection is presented in Fig. 6.6. Review Manager 5.1 was employed for data analysis. RR with 95% CI was used with fixed- or random-effect models, depending on heterogeneity (172).

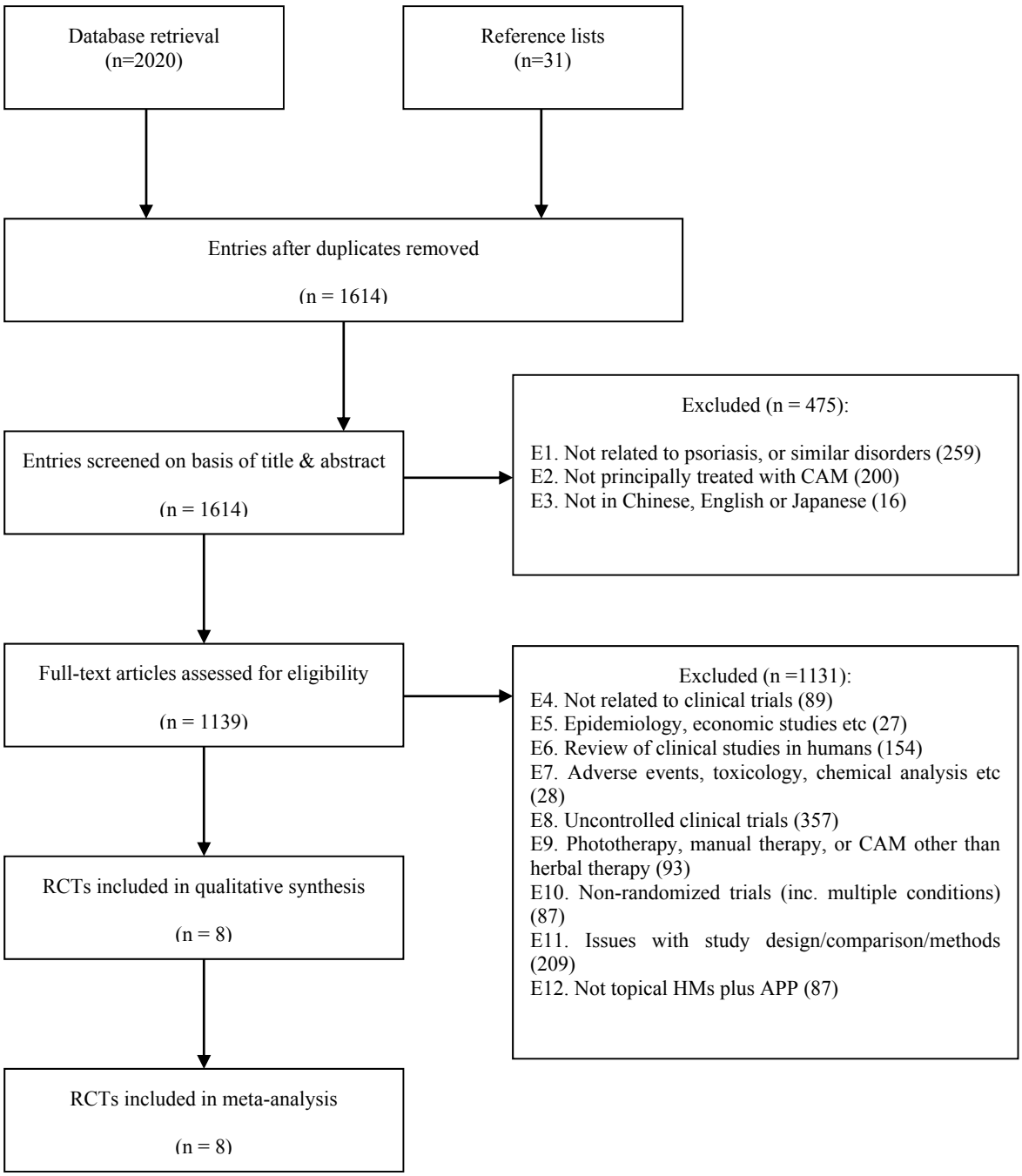


Fig. 6.6 Flow chart of the selection process of randomised controlled trials (RCTs) of external herbal medicines (HMs) combined with anti-psoriatic pharmacotherapy (APP) [adapted from Deng 2013 (157)]

6.3.3 Results

6.3.3.1 Description of studies

In total, 2,020 potential entries were obtained from the database searches and 31 studies were identified from reference lists. After removal of duplicates, the remaining 1,614 records were screened and the full text of 1,139 entries was obtained. Among these, 8 articles satisfied the inclusion criteria (Fig. 6.6) (238-245). All the RTCs found were conducted in China. The studies enrolled 1,449 participants and 1,446 completed the trials (Table 6.6). The following HM interventions were used: baths (n=4), ointments (n=3) and steam (n=1). All participants used APPs. *S. baicalensis* root (Huang qin), *S. flavescens* root (Ku shen), *Cnidium monnieri* seed (She chuang zi), *D. dasycarpus* bark (Bai xian pi) and borneol (bing pian) were each used in 3 studies. *S. baicalensis* root, *Rheum palmatum* root (Da huang), *Rehmannia glutinosa* root (Di huang), *Salvia miltiorrhiza* root (Dan shen), *Carthamus tinctorius* flower (Hong hua) and sulphur were each used in 2 studies (Table Ch6.6). Somewhat surprisingly, *Indigo naturalis* (Qing dai), which is frequently used as an external HM for psoriasis, was not included in any of the 8 formulations (246).

Table 6.6 Characteristics of the 8 studies included in analysis [adapted from Deng 2013 (157)]

First author, Publication year, Location, Duration, Follow-up	**Sample size (R/A), Gender (M/F), Age (yrs): Mean ± SD (Range), RCT Design (T vs C)**	**HM: ingredients (scientific name, part), dosage & administration**	**APP dosage & administration**	**Diagnosis, Outcome measures, Results**	**Dropouts, Adverse events (AEs)**	**Risk of Bias (SG, AC, BPt, BPl, BOA, IOD, SOR)**
Feng, Y. J., 2007; Beijing, China; 3 weeks; NS	T: 32/32, C: 33/33; 57/8; 38 yrs (10-60); HM + ext. APP vs ext.APP.	Herbal bath: *Fengfang* (*Polistes mandarinus* nest), *Xiqiancao* (*Siegesbeckia orientalis* herb), *Digupi* (*Lycium barbarum* root), *Shengdi* (*Rehmannia glutinosa* root), *Tougucao* (*Impatiens balsamina* herb) each 50g, *Kushen* (*Sophora flavescens* root), *Baixianpi* (*Dictamnus dasycarpus* bark) each 40 g, *Danshen* (*Salvia miltiorrhiza* root), *Shechuangzi* (*Cnidium monnieri* seed) each 30 g, *Honghua* (*Carthamus tinctorius* flower) 20 g. in 2000 ml water, 20 mins, 1 X day, for 3 weeks	*Kangminzhiyang* cream (Triamcinolone acetonide), 2 X day, Ammonium glycyrrhizinate IV solution 150mg/day	Psoriasis vulgaris. Reduction in lesion area T>C (χ^2 =5.54, p=0.019); Clearance time T<C (t=4.32, p=0.001); Lesion score: itching T<C (t=2.72, p=0.008), scaling T<C (t=2.84, p=0.006), erythema & induration (not sig)	No dropouts; AEs: slight dizziness & palpitation (T:2)	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Han, C. L., 2006; Dongwan, China; 3 weeks; 1 month	T: 43/43, C: 32/32; NS; NS; HM + ext. APP vs ext. APP	Commercial *Binghuangfule* ointment manufactured by Tibet GiGi Pharmaceutical Co., Ltd.: *Dahuang* (*Rheum palmatum* root), *Jianghuang* (*Curcuma longa* root), *Liuhuang* (sulphur), *Huangqin* (*Scutellaria baicalensis* root), *Gancao* (*Glycyrrhiza uralensis* root), *Bingpian* (borneol), *Bohe* (*Mentha haplocalyx* leaf), etc. 1 X day	Clobetasol cream, 1 X day (compounded by the hospital)	Psoriasis vulgaris. PASI T≈C (t=0.327, p>0.05); Overall clinical efficacy‡ T≈C (χ^2 =0.040， p>0.05); Follow up relapse: T. 5 (26.32%), C. 8 (47.06%)	No dropouts; AEs: skin pigmentation (C:1), hypopigmentation & skin atrophy(C:2), Malassezia folliculitis (C:3), skin pigmentation (T:2)	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Liu, X. J.,	T: 42/42, C:	Commercial *Binghuang* ointment	0.5% tazarotene gel	Stable psoriasis	No dropouts;	SG: U

2012; Huangshi, China; 4 weeks; NS	42/42; T: 22/20, C: 19/23; T: 28.5 yrs (5-65), C: 29.6 yrs (10-68); HM + ext. APP vs ext. APP	manufactured by Shenyang Jinlong Pharmaceutical Co., Ltd. (Batch 20090301): *Dahuang* (*Rheum palmatum* root), *Huanglian* (*Coptis chinensis* root), *Liuhuang* (sulphur), *Bingpian* (borneol), etc. 1 X day (night), for 4 weeks	manufactured by Chongqing Huapont Pharm. Co. Ltd. (Batch 20040124). 2Xday, for 4 weeks	vulgaris. Reduction in PASI: T>C (p<0.05)	AEs: slight itching & burning (T:3, C:5)	AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Tang, Y. Y., 2004; Hangzhou, China; 10 times (over 10-20 days); NS	T: 36/36, C: 36/36; T: 23/13, C: 26/10; T: 42.33 yrs ± 13.78, C: 41.72 yrs ± 13.66; HM + ext. APP vs ext. APP.	Herbal bath: *Shengdi* (*Rehmannia glutinosa* root), *Kushen* (*Sophora flavescens* root), *Danggui* (*Angelica sinensis* root), *Chishao* (*Paeonia veitchii* root), *Baixianpi* (*Dictamnus dasycarpus* bark) and *Pugongying* (*Taraxacum mongolicum* herb), each 60g of raw herbs. In warm bath, 1:40,000, 30 mins 1 X day or 1 X 2 days, total 10 X as a course	Dexamethasone liniment, Salicylic acid ointment, & Triamcinolone acetonide acetate ointment, Slow injection of procaine* 4-6 mg/kg plus vitamin C 300mg in 300 ml saline once a day for 10-15 days as a course, Warm water bath 1 X day or 1 X 2days (only for Control group)	Psoriasis vulgaris. Overall clinical efficacy T>C (χ^2 =5.796，p<0.05)	No dropouts; AEs: NS	SG: U AC: U BPt: H BPl: H BOA: U IOD: L SOR: L
Wang, M., 1990; China; 24.7 days[#]; 1 year	T:675/675, C:200/200; T: 612/63, C: NS; T: 18-49 yrs, C: NS; HM + ext. APP vs ext. APP.	*Yin Xie Ling* ointment: *Huangqin* (*Scutellaria baicalensis* root) extract 39g, *Diyu* (*Sanguisorba officinalis* root) extract 59g and *Huangbai* (*Phellodendron amurense* bark) extract 29g, 0.3 mm thickness, 1 X day	Dichlorodiethyl sulphide (1:10000 in petroleum jelly), 0.3 mm thickness, 1 X day	Psoriasis. Overall clinical efficacy T>C (90.7%>84%, p<0.05); Mean inpatient time to lesion clearance T<C (24.7<32.5 days); Follow up relapse: T<C (13%<76%)	No dropouts; AEs: allergic response rate T<C (1.93%<5%)	SG: U AC: U BPt: U BPl: U BOA: U IOD: L SOR: L
Wang, H. Y., 2010; Changchun, China;	T: 22/22, C: 20/20; 34/8; 37.6 yrs ± 15.1	Herbal bath: *Kushen* (*Sophora flavescens* root) 30g, *Aiye* (*Artemisia argyi* herb) 30g, *Shechuangzi* (*Cnidium monnieri*	Salicylic acid cream 2Xday, Methotrexate, oral 5-15 mg/week	Psoriasis vulgaris. Overall clinical efficacy[‡]	No dropouts; AEs: hair loss (T:1), slightly increased ALT	SG: U AC: U BPt: H BPl: H

6 weeks; NS	(18-58); HM + ext. & int. APP vs ext. & int. APP.	seed) 30g, *Baijiangcao* (*Patrinia villosa* herb) 30g, *Mudanpi* (*Paeonia suffruticosa* root bark) 20g, *Baixianpi* (*Dictamnus dasycarpus* bark) 30g, *Danshen* (*Salvia miltiorrhiza* root) 20g, *Cebaiye* (*Biota orientalis* leaf) 30g, *Wubeizi* (*Rhus chinensis* gall) 30g, *Baibu* (*Stemona sessilifolia* root) 10g, etc. As 3000 ml bath for 20-30 mins 1 X day for wks 1-2, then 1 X 2 days for wks 3-4, then 2Xwk for wks 5-6		T>C (χ^2 =8.24, p<0.05)	(T: 1=50U/L, C: 1=55U/L), stomach discomfort (T:1, C:2)	BOA: U IOD: L SOR: L
Yang, H. Y., 2008a; Xiangfan, China; 4 weeks; 6 months	T: 82/82, C: 50/47; 83/49; (15-75 yrs); HM + ext. APP vs ext. APP.	Herbal bath: *Huajiao* (*Zanthoxylum bungeanum* seed), *Kufan* (Alumen) each 120g, *Yejuhua* (*Chrysanthemum indicum* flower) 250g, and *Puxiao* (Mirabilite) 500g, decocted in water adequate for a body bath. Frequency of use not specified.	Halcinolone acetonid cream 2 X day, Thymosin IV solution 40mg/day	Psoriasis vulgaris. Overall clinical efficacy‡ T>C (χ^2 =4.649, p<0.05) Follow up relapse: T. 1 (3.55%), C. 2 (18.2%)	3 dropouts; AEs: no obvious issues	SG: H AC: U BPt: H BPl: H BOA: U IOD: U SOR: L
Yang, X. Q., 2008b; Luzhou, China; 4 weeks; NS	T: 58/58, C: 46/46; T: 35/23, C: 25/21; 35.8 yrs (20-68); HM + ext. & int. APP vs ext. & int. APP.	Herbal steam: *Ezhu* (*Curcuma phaeocaulis* rhizome) 50g, *Cangzhu* (*Atractylodes lancea* root), *Shechuangzi* (*Cnidium monnieri* seed), *Sanleng* (*Sparganium stoloniferum* root) each 30g, *Bingpian* (Borneol) 3g, *Honghua* (*Carthamus tinctorius* flower) 15g, *Houpo* (*Magnolia officinalis* bark) 20g, *Dingxiang* (*Syzygium aromaticum* fruit) 6g, etc. with additions according to individual syndromes. Applied using specific device, 20 mins/day for 5 days, 2 days break, for 4 wks as a course	Hydrocortisone butyrate cream 2 X day, Urea cream 2 X day, Acitretin capsules, oral 30-40 mg 1 X day	Psoriasis vulgaris. Overall clinical efficacy‡ T>C (χ^2 =9. 91, p<0.01)	No dropouts AEs (T/C): dry mouth, dry lips & chapped lips (44/46), dry eyes (28/38), dry skin on body (22/34), epistaxis (4/6), body itching (13/19), desquamation (11/25), increased ALT (2/8), hyperlipidemia (1/1)	SG: H AC: U BPt: H BPl: H BOA: U IOD: L SOR: L

T: treatment group, C: control group, R/A: registration/analysis, M/F: male/female, NS: not stated, IV: intravenous injection, ext.: external, int.: internal, yrs: years, wks: weeks, mins: minutes, RCT: randomised controlled trial, HM: herbal medicine, APP: anti-psoriatic pharmacotherapy, ALT: alanine aminotransferase, PASI: Psoriasis Area and Severity Index

*Procaine plus vitamin C injection is used in China for itchy skin in diseases such as neurodermatitis (247, 248). It is thought to restore the normal metabolic function of skin cells and relieve erythema and itching. Using this method, corticosteroid-induced complications and side effects can be avoided (249).
#Average inpatient period for cleared participant
‡Clinical efficacy scores based on PASI using the following formula: (PASI pre-care − PASI post-care)/PASI pre-care × 100%

Risk of Bias Categories
SG: sequence generation, AC: allocation concealment, BPt: blinding of participants, BPl: blinding of personnel, BOA: blinding of outcome assessment, IOD: incomplete outcome data, SOR: selective outcome reporting

Risk of Bias Judgements
L: low risk, U: Unclear risk, H: high risk

Two studies reported full details of diagnosis and inclusion/exclusion criteria for subject selection (240, 242); 3 studies described the inclusion/exclusion criteria (238, 239, 245) and 3 studies provided no details of these methods (241, 243, 244). Details of Chinese medicine diagnosis were provided by 1 study (240). Adjustments of the herbal formula or assessment of the clinical efficacy according to the Chinese medicine diagnosis was performed in 3 studies (238, 241, 245). No quality-control data were supplied in any of the studies.

Clinical efficacy was variously reported as clinical efficacy based on PASI scores, clinical efficacy according to a national standard for Chinese medicine (241) or a similar system (243) or separate scores for lesion characteristics (238).

Herbal baths plus APP vs APP (4 studies)

In the study by Feng *et al.* (238), 32 psoriasis vulgaris in-patients were treated with a herbal bath and APP, while 33 patients were treated with APP alone (Table 6.3). Patients soaked themselves in the bath for 20 min, once a day for 3 weeks. Patients in both the groups were administered ammonium glycyrrhizinate IV solution and triamcinolone acetonide cream (250). In the combined therapy group, statistically significant improvements in the extent of itching and scaling were found after 1 week. Compared with the control group, the overall clinical efficacy and time to clearance in this group improved after 3 weeks.

In the study by Tang (241), 36 patients soaked themselves in a herbal bath for 30 min once a day or once every 2 days. The control group (36 patients) had a warm water bath. Both the groups received slow IV injections of procaine plus vitamin C; dexamethasone liniment, salicylic acid ointment and triamcinolone acetonide acetate ointment were also applied. The HM group showed a greater reduction in lesion areas after 10 treatments (over 10–20 days) than the control group.

A different herbal bath formula was used by Wang *et al.* (242); 22 patients soaked themselves in the bath for 20–30 min daily for weeks 1–2, once every 2 days for weeks 3–4 and twice a week for weeks 5–6. All 42 patients used MTX and salicylic acid cream. The study revealed a significant difference between overall clinical efficacies in the experimental and control group. The efficacy was calculated on the basis of the reduction in PASI scores.

Yang *et al.* (244) examined the results of treatment with a herbal bath plus thymosin IV

solution and halcinolone acetonide cream involving 132 psoriasis vulgaris patients. After 4 weeks, a difference was observed between groups, with the HM group performing better than the controls. During the 6-month follow-up, 3 patients who had achieved 'clearance' (95% improvement) relapsed: 1 in the test group and 2 in the control group.

Herbal steam plus APP vs. APP (1 study)

In the study of Yang *et al.* (245), 58 patients were treated with herbal steam using a steaming device for 20 min a day for 5 days, followed by a 2-day break, during a 4-week course. All patients in both the groups (104 patients) were treated with acitretin capsules, urea cream and hydrocortisone butyrate cream. After 4 weeks, there was a significant difference between overall clinical efficacies in the combined therapy group and APP group.

Herbal ointment plus APP vs. APP (3 studies)

An ointment containing extracts of 3 herbs plus 0.05 ml of dichlorodiethyl sulphide was used by 675 patients in the study of Wang *et al.* (243). The results were compared with those for 200 patients who used 0.10 ml of dichlorodiethyl sulphide ointment alone. There was a significant benefit in using the test ointment in terms of the overall clinical efficacy, allergic response rate, mean inpatient time to lesion clearance and 1-year recurrence rate. The authors concluded that the test ointment, which used 50% less dichlorodiethyl sulphide, showed a higher efficacy and caused fewer allergic side effects than the standard therapy.

The efficacy of a commercial ointment (Binghuangfule) used with clobestasol cream was assessed by Han *et al.* (239) versus clobestasol cream alone. Patients in the HM group applied the herbal ointment and clobestasol cream once a day. Those in the control applied clobestasol cream twice a day. After 3 weeks of treatment, no significant differences were observed between PASI values or overall clinical efficacy levels in the 2 groups. However, significantly fewer side effects were observed in the combined therapy group. The authors concluded the combined treatment had a similar curative effect to clobestasol cream but had fewer side effects due to the reduced dose of clobestasol.

A comparison study between the effects of a similar commercial ointment (Binghuang) used with 0.5% tazarotene gel and 0.5% tazarotene gel alone was conducted by Liu *et al.* (240). Binghuang ointment was administered once each night and tazarotene gel was applied twice

a day. After 4 weeks, there was a difference between clinical efficacies (based on reduction of PASI score) in the 2 groups. Slight itching and burning were reported in both the groups (T = 3, C = 5). The authors concluded that the combination treatment showed better efficacy than 0.5% tazarotene gel alone.

6.3.3.2 Methodological assessment

Risk-of-bias evaluations are summarised in Table 6.6. The authors of all studies evaluated here stated that the trials were 'randomised' or used a similar expression. However, the method of sequence generation was not provided in 7 of the studies and 1 used a pseudo-randomisation method (patient's visiting order) (245). No study provided information on the method of allocation concealment or blinding. Seven studies used the design of HM plus APP versus APP; consequently, blinding to participants and personnel was not possible. In 1 study (243) all HMs were combined with the ointment used in the control group; blinding to participants was possible; however, it was not stated. One of the studies (241) used a warm water bath in the control group; this may have been intended as a form of participant blinding; however, this was not stated and was unlikely to have been effective. Three subjects dropped out in 1 study; however, no reasons were provided (244). Other studies reported that all patients completed the study; therefore, the risk of incomplete outcome data was low. All studies reported all outcomes; therefore, the risk of bias due to selective reporting was also low.

6.3.3.3 Meta-analysis

The comparisons in 6 of the studies (238-241, 243, 244) were mainly made between an externally applied HM combined with a external APP and the external application of APP alone (group 1). A topical treatment with HM plus a combination of external and internal APPs was compared with the combination treatment alone in 2 other studies (Group 2) (242, 245). These 2 studies are similar in terms of the study design and the used outcome measures; therefore, meta-analysis of pooled data was possible.

Results for clinical efficacy were analysed using RR and a random-effect model. Various group 1 studies used different systems for classifying the clinical efficacy. For example, in Feng *et al.* (238), lesion reduction of 75% and above was considered 'remarkably effective'; however, in Yang *et al.* (244) 'remarkably effective' referred to a reduction of 70%–95%.

Consequently, when pooling data, only cases with efficacy rates of 50% or more were included.

Both group 2 studies defined a PASI reduction of 60% or more as 'remarkably effective'; therefore, this became the threshold chosen for data pooling (242, 245). In meta-analyses, a higher score indicates greater efficacy.

Group 1. External HM + external APP vs. external APP

For 6 studies (238-241, 243, 244), increased efficacy rates were found for topical HM plus APP treatments in comparison with APP therapy alone (RR 1.18; 95% CI: 1.05–1.34). This result was consistent with the conclusions of the original studies, except for the study by Han (48), where similar efficacies were reported in the test and control groups (Fig. 6.7). However, the heterogeneity in this study was high (I^2 = 63%).

Group 2. External HM + external & internal APP vs. external & internal APP

For the 2 studies in this group (242, 245), the pooled data showed higher efficacy for the external HM plus APPs in comparison with APP treatment alone (RR 1.67; 95% CI: 1.21–2.30). This result was consistent with the conclusions of the authors (Fig. Ch. 6.7) and the heterogeneity was low (I^2 = 0%).

Overall, in the 8 studies, the efficacy of combined external HM and APP treatment was significantly higher than that of APP alone (RR 1.23; 95% CI: 1.09–1.40) (Fig. 6.7).

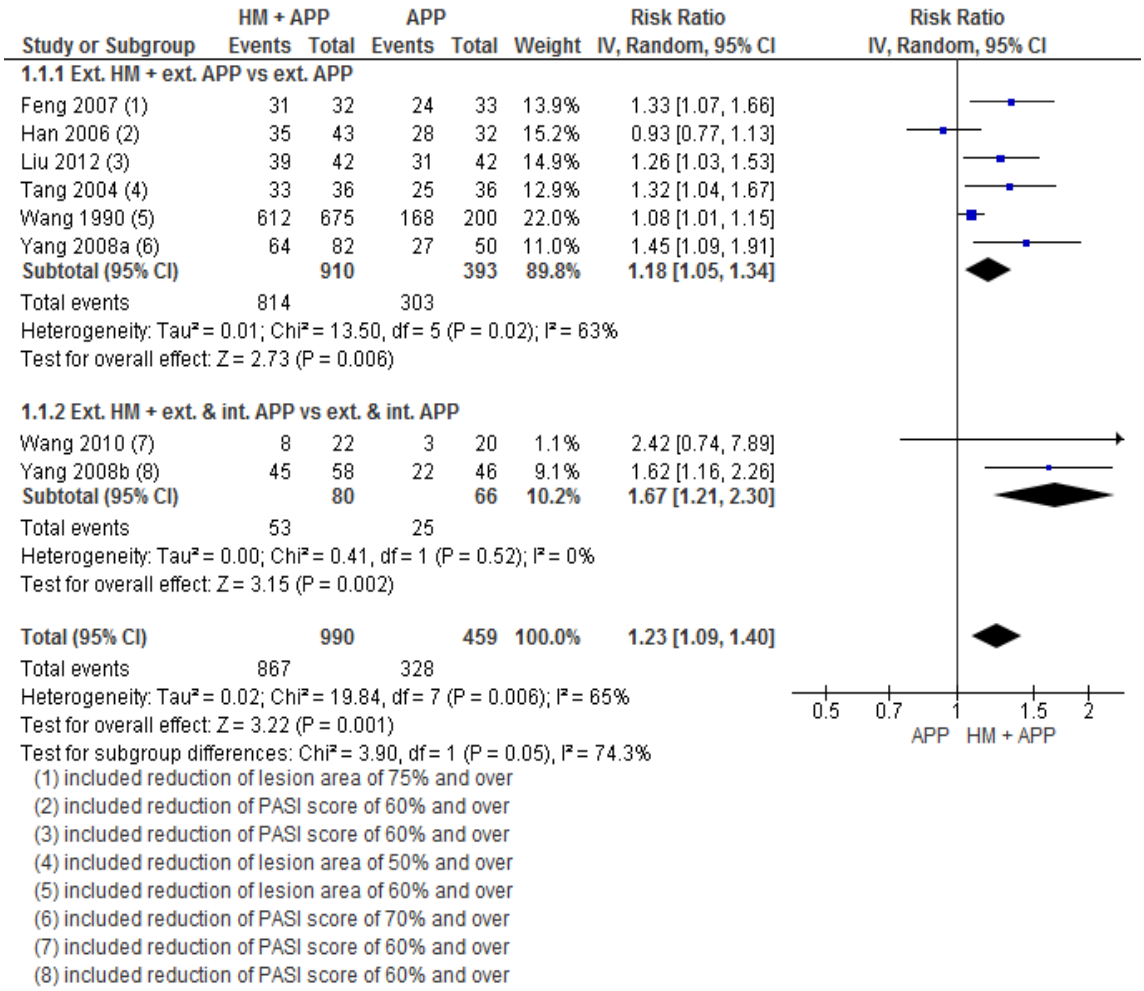


Fig. 6.7 Forest plot of clinical efficacy: external herbal medicine (HM) plus anti-psoriatic pharmacotherapy (APP) versus anti-psoriatic pharmacotherapy (APP) [adapted from Deng 2013 (157)]

6.3.3.4 AEs

Seven studies provided a report on AEs and 1 provided no information (241). One study stated that no remarkable AEs occurred in either the test or control group (244). Yang *et al*. (245) reported that AEs were significantly fewer in the combined therapy group than in the control group, with the exception of epistaxis and the level of serum lipids, which did not differ. In the study of Feng *et al*. (238), 2 cases of mild dizziness and palpitations were reported in the experimental group; however, no information was provided for the control group. In the 5 studies supplying complete data, the incidence of AEs was lower in the combination therapy groups [4.65% vs. 18.8% (239); 7.14% vs. 11.91% (240), 1.93% vs. 5% (243); 13.6% vs. 15.0% (242) and 75.9% vs. 100% (245)] than in control groups. Reported

AEs were mostly local disorders (239, 245); however, there were reports of dizziness, palpitations, stomach discomfort, epistaxis and hyperlipidaemia. Abnormal alanine aminotransferase (ALT) was reported in two studies (242, 245); however, meta-analysis revealed no difference in its incidence between groups (RR 0.28; 95% CI: 0.08–1.05) (Fig. 6. 8).

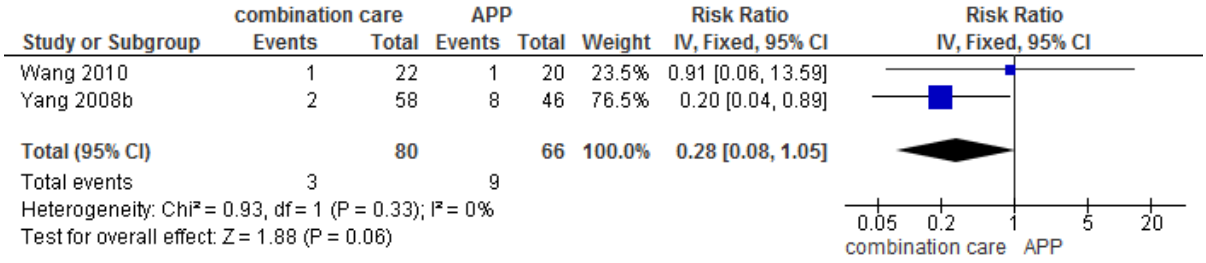


Fig. 6.8 Forest plot of severe adverse events (ALT↑): external herbal medicine (HM) plus anti-psoriatic pharmacotherapy (APP) versus anti-psoriatic pharmacotherapy (APP)

6.3.5 Discussion

Each of the 8 RCTs found benefits in the use of combination therapy in comparison with the use of APP treatment alone. However, reporting methodology was inadequate, and none of the studies was effectively blinded. Admittedly, blinding presents practical difficulties when herbal baths or decoctions are used. However, without blinding, it is not possible to draw clear conclusions; the observed benefit may have been due to HM or an additional intervention.

Combining HM and APP can address the side effects of long-term APP use. To minimise side effects, the clinicians can reduce the dose of medication or replace it with another drug. Wang *et al*. (243) adopted both approaches by reducing the concentration of dichlorodiethyl sulphide, which can cause skin erosion, while adding 2 herbs to the test ointment. Han *et al*. (239) reduced the APP dose by using the topical HM ointment and APP cream alternately. In the other 6 studies, the approach was to provide additional therapy in the form of baths, steam or ointment. Some studies used APPs of questionable clinical efficacy (238, 241, 244), which added further limitations to the interpretation of results.

Meta-analysis of clinical efficacy for group 1 revealed high heterogeneity; variation in outcome measures, sample sizes and control interventions were the likely cause. Group 2 trials used PASI and employed APP interventions that better reflected the established

treatment methods. The results of group 2 studies are particularly relevant to contemporary clinical practice. In one of these studies, Yang *et al*. (245) showed the superiority of combination therapy (HM + acitretin) over the conventional APP treatment; however, the study of Wang *et al*. (242) (HM + MTX) appears to be of a better quality.

Combination therapies of the types described in these studies are often used in China. The possible effects of the herbal ingredients such as *S. flavescens*, *C. monnieri*, *D. dasycarpus* and borneol are of considerable interest and will be discussed in the next chapter.

Some orally administered herbal decoctions containing *Dictamnus* root have been reported to cause acute hepatitis (187-190). Only 2 cases of mild skin sensitisation were found (n = 25) when using 20% *l*-borneol in petrolatum, and no significant skin irritation was revealed (251). There are no reports of toxicity associated with the topical use of *Dictamnus* root bark, *Cnidium* seed, *Sophora* root, *Phellodendron* bark, *Scutellaria* root or *Coptis chinensis*.

6.3.6 Summary

This review shows that the addition of HMs to APP treatment can result in short-term efficacy improvements in comparison with APP therapy alone. However, the data need to be interpreted with caution; the trials assessed here had some methodological weaknesses and there are no independent studies confirming the results. These methodological deficiencies should be addressed in future studies investigating the efficacy and safety of HMs as adjunctive therapies for psoriasis.

6.4 Conclusions regarding the external HM RCTs for psoriasis

Clinical studies examined here suggest that combined treatment including topical application of CHM may be beneficial in controlling psoriasis symptoms. Although there are methodological flaws in each of the included studies, recent experimental evidence indicates that some herbs used in these studies have anti-inflammatory, anti-pruritic and anti-proliferative activities. Although this experimental evidence is mostly based on systemic use, it supports the traditional use of these herbs in the topical management of psoriasis.

Chapter 7: Investigation of the *in vitro* and *in vivo* actions of the main herbs

7.1 Introduction to Part 2

In Part 1 of the thesis, the methodology of the systematic review was used to evaluate the efficacy and safety of HMs used topically (three SRs (157-159)) and systemically (one SR (135)) for psoriasis vulgaris. In addition to the usual approach employed in SRs of HMs, when multi-herb formulations were employed, the herbs that were most commonly used were identified. This approach allowed the identification of specific herbs for which there was promising clinical evidence of efficacy.

In Part 2 of the thesis, the mechanisms of action of the most promising herbs are explored in order to provide directions for further drug discovery investigations and to inform the design of future clinical trials. Part 2 involved the following three main components:

1. Analysis of the *in vivo* & *in vitro* studies on HMs (chapter 7),
2. Identification of herbs that share therapeutic targets with APPs, i.e. APP-like herbs, and exploration of the possible pathways of action of the HMs (chapter 8),
3. General discussion and further directions (chapter 9).

Each of these components presents a method for adding meaning and value to the results of the systematic reviews undertaken in Part 1 and each component also explores and develops methods that could be applied to other SRs of HMs. These approaches can link the clinical trial evidence with *in silico* methods of investigation that focus on the possible mechanisms of action of the HM and could provide indications of futre directions in drug discovery and clinical studies.

In chapters 8 and 9 the methods and procedures for each of these components are separately described in detail followed by the results.

7.2 Method for *in vivo* & *in vitro* studies

The first step in this component involved the selection of the most promising herbs. Promising herbs were defined as the herbs for which there was evidence of clinical efficacy

and safety based on the results of the SRs. Since there were many herbs employed in the studies that were included in the studies in each of the SRs, the most promising herbs were selected based on frequency of use in the RCTs, with up to four of the most frequently used herbs being selected from each of the four SRs.

The second step involved database searches for experimental studies that evaluated the *in vivo* and/or *in vitro* effects of these herbs and/or their constituents as regards actions that are relevant to psoriasis. Relevance was broadly defined as having effects on inflammation, proliferation, angiogenesis, pruritus, wound healing and/or tissue repair.

Studies could employ herbal extracts, fractions or purified forms of compounds known to be major active components of the herbs. Experimental models were not limited to psoriasis but studies that employed keratinocytes or were otherwise focused on skin were preferentially selected.

Articles located in the initial searches that had been classified as experimental studies were examinined and additional searches were conducted of PubMed in July 2013 using search terms for the plant names, for example: oldenlandia, hedyotis, bai hua she she cao; and compounds, for example: ursolic acid, oleanolic acid. No restrictions were placed on year, article type or language. Potentially relevant articles were identified based on scanning abstracts and full texts were obtained. Data were extracted from relevant articles by SD and BHM to a spreadsheet.

A narrative method was used for data synthesis that focused on the studies most relevant to herbal therapy for psoriasis. Therefore this chapter does not summarise every experimental study on every herb and every compound contined in the herb.

7.3 Results for *in vivo* & *in vitro* studies of the anti-psoriatic actions of the main herbs

Based on the results of the four SRs, 13 herbs were identified as showing promise of efficacy for psoriasis as well as having acceptable safety profiles. These are listed in Table 7.1. One herb appeared in the lists of herbs in two SRs, so 12 different herbs were identified. The results of the *in vivo* and *in vitro* studies for these herbs are presented and discussed below for each SR separately. The names of proteins and drug targets are multiple and the same protein may receive different names and aconyms in different publications.

Consequently a list of the various names used in chapters 7 and 8 is included in Appendix 20.

Table 7.1: Promising herbs for psoriasis based on the results of systematic reviews of RCTs

Scientific name	**Chinese character**	**SR, study design, admin.***
Oldenlandia diffusa	白花蛇舌草	SR1, Herbal formula vs APP/placebo, int.
Rehmannia glutinosa	地黄	SR1, Herbal formula vs APP/placebo, int.
Salvia miltiorrhiza	丹参	SR1, Herbal formula vs APP/placebo, int.
Aloe vera	芦荟	SR2, Single herb vs APP/placebo, ext.
Indigo naturalis	青黛	SR2, Single herb vs APP/placebo, ext.
Camptotheca acuminata	喜树	SR2, Single herb vs APP/placebo, ext.
Mahonia aquifolium	功劳木	SR2, Single herb vs APP/placebo, ext.
Sophora flavescens	苦参	SR3, Herbal formula vs APP/placebo, ext.
Lithospermum erythrorhizon	紫草	SR3, Herbal formula vs APP/placebo, ext.
Sophora flavescens	苦参	SR4, HM + APP vs APP, ext.
Cnidium monnieri	蛇床子	SR4, HM + APP vs APP, ext.
Dictamnus dasycarpus	白藓皮	SR4, HM + APP vs APP, ext.
Borneol	冰片	SR4, HM + APP vs APP, ext.

* this refers to the administration route in the included studies. In clinical practice multiple routes may be used.

7.4 Anti-psoriatic actions of the main herbs identified in SR1: medicinal herbs used internally for psoriasis (7.4.1-7.4.3)

In this SR, three plants were each used in 5 studies: *Rehmannia glutinosa* Libosch, root; *Salvia miltiorrhiza* Bge., root; and *Oldenlandia diffusa* (Willd.) Roxb. [*aka Hedyotis diffusa*], aerial parts. The pharmacological actions of the above identified herbs in the experimental studies are individually summarized in the tables 7.2-7.4.

7.4.1 Experimental studies of *Oldenlandia diffusa* (bai hua she she cao)

Oldenlandia diffusa mainly contains anthraquinone, terpenoids, flavonoids, sterols, alkanes, organic acids, polysaccharides, alkaloids, diffusa prime, cardiac glycosides as well as some trace elements, amino acids and volatile ingredients (252).

The anti-proliferative effect of a 70% ethanol extract of *Oldenlandia diffusa* was investigated by Gu *et al* 2012 in normal breast epithelial cells (MCF-10A) and in four human breast cancer cell lines (MCF-7, T47-D, SKBR3, & tamoxifen resistant MCF-7 TRI cells). The extract reduced cell viability in MCF-7 cells but not in normal MCF-10A cells. It also inhibited proliferation in MCF-7 and estrogen receptor (ER)-positive T47-D cells but not in ER-negative SKBR3 breast cancer cells. The anti-proliferative action in MCF-7 cells was via increasing p53 [Cellular tumour antigen] and $p21^{WAF1/Cip1}$ [Cyclin-dependent kinase inhibitor 1] protein expression and inducing apoptosis. Following fractionation, two bioactive compounds were identified, oleanolic and ursolic acids, which showed similar effects in the above cell lines. Moreover, the combination of oleanolic acid or ursolic acid and tamoxifen reduced proliferation in tamoxifen resistant MCF-7 TRI cells. The extract also up-regulated p53 and $p21^{WAF1/Cip1}$ expression of MCF-7 in an ERa/Sp1-dependent manner (253).

In an *in vitro* study, ursolic acid isolated from *Oldenlandia diffusa* showed cytotoxicity against SK-OV-3 and A2780 ovarian cancer cells with IC_{50} of *ca.* 50 and 65μM, respectively. In SK-OV-3 ovarian cancer cells, ursolic acid up-graduated Sub-G1 Apoptotic Portion, activated Caspase-9 and Caspase-3, cleaved Poly (ADP-ribose) polymerase (PARP), down-regulated the expression of Survival Genes, and induced the apoptosis of SK-OV-3 ovarian cancer cells. The regulation mechanism could relate to the activation of caspases and phosphorylation of glycogen synthase kinase 3β (GSK 3β) (254).

Ursolic acid induced apoptosis in a doxorubicin-resistant human hepatoma cell line (R-HepG2) via disruption of mitochondrial membrane potential, activating Bak protein [Bcl-2-associated X protein], and release of AIF [apoptosis-inducing factor] – a signalling pathway irrelevant to caspase. In a 3-group *in vivo* study of female nude mice subcutaneously inoculated with R-HepG2 cells, ursolic acid significantly reduced tumour volume by 53.13% (50 mg/kg UA group) and 66.10% (75 mg/kg UA group) ($P < 0.01$) with no significant weight loss or toxicity (based on spleen index). Immunohistostaining attested

accumulation of AIF in the nucleus. Therefore, ursolic acid showed potent anti-proliferative activity with no obvious toxicity (255). Harmand *et al* 2005 investigated the effect of ursolic acid in M4Beu human melanoma cells and reported that found that ursolic acid induced apoptosis via the activation of caspase-3 (256). In a mouse skin cancer model, Kowalczyk *et al* 2009 tested a number of phytochemicals and found that ursolic acid reduced epidermal hyperplasia and reduced the rate of mutations in codon 61 of Ha-ras oncogene in mouse skin (257). Wojciak-Kosior *et al* 2011 compared the effects of ursolic and oleanolic acid on normal human skin fibroblasts and found that ursolic acid had greater free radical scavenging activity as well as higher cytotoxicity compared to oleanolic acid (258).

In a lipopolysaccharide (LPS)-induced inflammation model in male C57BL/6 (6 week old) mice peritoneal macrophages, pre-treatment with an aqueous extract of *Oldenlandia diffusa* inhibited production of TNF-α [Tumour necrosis factor-alpha], IL-6 [interleukin 6], PGE_2 [prostaglandin E_2] (significantly and dose-dependently). It also inhibited the enhanced expression of COX-2 [cyclooxygenase-2], NO [nitrogen oxide] (dose-dependently), iNOS [inducible Nitric oxide synthase], $I_\kappa B$-α [ikappaB kinase] (significantly) in response to the LPS. Hentriacontane which was derived from the *Oldenlandia diffusa* significantly inhibited expression of the inflammation mediators TNF-α, IL-6, PGE_2 and COX-2 as well as suppressed NF-$_\kappa$B [nuclear factor kappa-light-chain-enhancer of activated B cells] and caspase-1 (259). In female mice with dextran sulfate sodium (DSS)-induced colitis, an aqueous extract of *Oldenlandia diffusa* significantly relieved the clinical signs including weight loss and colon shortening, and remarkably decreased Disease Activity Index (DAI). It also inhibited IL-6, IL-1β [interleukin 1beta] and COX-2 levels. In addition, the oral administration of the extract significantly inhibited the activation of NF-$_\kappa$B p65 [Transcription factor p65] in colitic tissues which had been induced by DSS. Similarly, the compound, hentriacontane, significantly suppressed the clinical signs and inhibited IL-6 level *in vivo* (260).

Kang *et al* 2008 investigated the effects of ursolic acid in a zymosan-induced acute inflammation model in mice. They found that oral ursolic acid suppressed leucocyte migration and it suppressed PGE_2 production dose-dependently. In a Freund's adjuvant-induced arthritis model in rats, the same group reported that oral ursolic acid reduced paw swelling, reduced the level of plasma PGE_2 and reduced hyperalgesia. They concluded that the effect of ursolic acid was comparable to that of ibuprofen (261).

Oleanolic acid acetate (OAA), which is a triterpenoid closely related to oleanolic acid that is derived from *Vigna angularis* (Willd.) Ohwi & H. Ohashi, was investigated in atopic dermatitis (AD) and allergic contact dermatitis (ACD) models in female mice. In the AD model, oral OAA dose-dependently reduced epidermal and dermal thickness in the ear, suppressed the infiltration of eosinophils, $CD4^+$ T cells, mast cells and serum histamine. It also reduced the levels of IgE [immunoglobulin E] (total and DFE-specific) and IgG2a [Immunoglobulin G2a]. It also suppressed the expression of pro-inflammatory cytokines and chemokines (TNF-α, IFN-γ [interferon-gamma], IL-4 [interleukin 4], IL-5 [interleukin 5], IL-10 [interleukin 10], IL-31 [interleukin 22], IL-17 [interleukin 17], IL-22 [interleukin 22]) and thymic stromal lymphopoietin (TSLP). In the ACD model, OAA suppressed lymphocyte proliferation in auricular draining lymph nodes in a dose-dependent manner. Serum IgG2a level, and some pro-inflammatory cytokines (TNF-α, IFN-γ and IL-17) were also suppressed by OAA but it only slightly inhibited other cytokines (IL-4 and IL-10), which demonstrated that OAA has a higher inhibitory effect of the immune reaction for Th1 and Th17 but not for Th2. No change in body weight was induced in either model. Finally, in human keratinocytes (HaCaT cells) pretreatment with OAA inhibited the effect of TNF-α/ IFN-γ induced gene expression of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and the chemokine TARC [Thymus and activation regulated chemokine] without reducing cell viability. Western blot analysis indicated that the mechanism of OAA action was via blocking the pathways of MAPKs (p38 [Activator of 90 kDa heat shock protein ATPase homolog 1], ERK [Extracellular signal-regulated kinase family] and JNK [Jun kinase]) and NF-$_\kappa$B (262).

Lim *et al* 2007 investigated the effects of oleanolic acid and ursolic acid on the recovery of epidermal barrier in mice and found that both compounds accelerated barrier formation. In normal human epidermal keratinocytes (HaCaT), these two compounds induced keratinocyte differentiation via actions on PPAR-α [peroxisome proliferator-activated receptor alpha] (263). Lee *et al* 2006, in a similar study, reported that found that both oleanolic and ursolic acids enhanced recovery of epidermal barrier function. Both compounds increased ceramide production but the effect of oleanolic acid on inducing keratinocyte differentiation was marked, whereas there was only a slight effect for ursolic acid (264).

None of the experimental studies located in the search was specific to psoriasis but they investigated actions of relevance to psoriasis therapy. The studies indicate that *O. diffusa*

contains compounds that have anti-inflammatory actions and can induce tissue repair in normal human skin cells. They can also inhibit proliferation in abnormal cells. Of the compounds contained in this plant, oleanolic acid and ursolic acid have been the object of considerable research attention. They have been shown to have liver protective, anti-tumour, anti-viral, anti-inflammatory, skin protective and anti-wrinkle effects. Synthetic derivatives of these compounds are currently the focus of drug discovery efforts (265-267).

Table 7.2 Summary of experimental findings on the actions of *Oldenlandia diffusa* [adapted from Deng 2013 (135)]

Preparation, Active ingredients	**Study type, Model examined**	**Outcome / Pharmaceutical target**	**Regulating effect**	**Reference**
ethanol extract, NS	*in vitro*: normal breast epithelial cells (MCF-10A)	p53 & $p21^{WAF1/Cip1}$	no effect	Gu 2012 (253)
	in vitro: human breast cancer cells (MCF-7)	p53 & $p21^{WAF1/Cip1}$, PARP (86 kDa)[§]	up	
oleanolic & ursolic acids	*in vitro*: human breast cancer cells (MCF-7)	p53 & $p21^{WAF1/Cip1}$	up	
ursolic acid	*in vitro*: SK-OV-3 & A2780 ovarian cancer cells	cytotoxicity against cancer cell (XTT assay)	IC50 of *ca*. 50 and 65 µM	Song 2012 (254)
	in vitro: SK-OV-3 ovarian cancer cells	sub-G1 apoptotic Portion	increased	
	in vitro: SK-OV-3 ovarian cancer cells	caspase-9 & -3, & cleaved PARP	activated	
	in vitro: SK-OV-3 ovarian cancer cells	expression of survival genes	down	
	in vitro: SK-OV-3 ovarian cancer cells	apoptosis	induced	
ursolic acid	*in vitro*: M4Beu melanoma cells	p21	not affected	Harmand 2005 (256)
		p53	altered: up then down	
		caspase-3	expression: up then down; activity: up	
		Bax & AIF	up	
ursolic acid	*in vivo*: zymosan-induced mice acute inflammation air pouch model	leucocyte migration, PGE_2	down	Kang 2008 (261)
	in vivo: Freund's adjuvant (CFA)-induced rat arthritis	PGE_2, FLI neurons	down	
ursolic acid	*in vitro*: Ca3/7 cell lines (squamous cell carcinoma)	caspase-3 & -7	up	Kowalczyk

	in vivo: female SENCAR mice with skin carcinogenesis	codon 61 of Ha-ras oncogene	down	2009 (257)
oleanolic acid (OA) & ursolic acid (UA)	*in vitro:* CV-1 & HaCaT cells	PPAR-α	OA: up; UA: not affected or slightly up	Lee 2006 (264)
	in vitro: HaCaT cells	CE formation of keratinocyte	OA: up; UA: slightly up	
	in vivo: hairless mice treated by absolute acetone	skin barrier recovery ceramide filaggrin & involucrin	enhanced up OA: up; UA: slightly up	
Oleanolic acid acetate (OAA)	*in vivo*: DFE/DNCB-induced AD model	ear swelling thickness	improved	Choi 2013 (268)
		body weight	nod changed	
		epidermal & dermal thickness, infiltration of eosinophils & $CD4^+$ T cells, infiltration of mast cells & serum histamine, IgE (total & DFE-specific) & IgG2a, all cytokines, TSLP (thymic stromal lymphopoietin) & chemokines, IFN-γ, IL-4, IL-17, IL-22	reduced/inhibited	
	in vivo: DNFB-sensitized ACD model	ear swelling thickness	improved	
		body weight	nod changed	
		lymphocyte proliferation, IgG2a, TNF-α, IFN-γ, IL-17, IL-4, IL-10	reduced/inhibited	
	in vivo: HaCaT cells	TNF-α, IL-1β, IL-6, TARC	reduced	
		cell viability	not effect	
ursolic acid (UA), oleanolic acid (OA)	*in vivo*: adult hairless mice with skin barrier disruption	skin barrier formation	accelerated	Lim 2007 (263)
	in vitro: human kertatinocytes (HaCaT)	PPAR-α & keratinocyte differentiation marker expression: involucrin, loricrin & filaggrin	up	
ursolic acid	*in vitro*: human hepatoma cell line (R-HepG2)	R-HepG2 proliferation bak	inhibited up	Yang 2010 (255)
	in vivo: female nude mice bearing R-HepG2 xenograft	tumour volume AIF	reduced up	

aqueous extract, NS	*in vitro*: mouse peritoneal macrophages with lipopolysaccharide (LPS) - induced inflammatory response	TNF-α, IL-6, PGE_2, COX-2, NO, iNOS, $I_\kappa B$-α, NF-$_\kappa$B activation, RIP-2/caspase-1 activation	down	Kim 2011 (259)
extract, NS	*in vivo*: dextran sulfate sodium (DSS)-induced colitis	clinical signs (weight loss, colon shortening, diarrhea, & occult/gross bleeding), Disease Activity Index (DAI), IL-6, IL-1ß & COX-2, NF-$_\kappa$B p65	reduced	Kim 2011 (260)
hentriacontane	*in vivo*: dextran sulfate sodium (DSS)-induced colitis	clinical signs, IL-6 Level	reduced	
ursolic acid (UA) & oleanolic acid (OA)	*in vitro*: normal human skin fibroblasts (HSF)	cytotoxicity (neutral red uptake, MTT test)	UA: toxic at over 5ìM. OA: no toxicity	Wójciak-Kosior 2011 (258)

α-SMA: α-smooth muscle actin; p21: Cyclin-dependent kinase inhibitor 1; p38: Activator of 90 kDa heat shock protein ATPase homolog 1; p53: Cellular tumor antigen; AIF: apoptosis-inducing factor; AP-1: activating protein-1; Bax protein: Bcl-2-associated X protein; Bcl-2 family proteins: B-cell lymphoma 2 family of apoptosis regulator proteins; CAT: catalase; CD: circular dichroism; $CD4^+$ T cells: T-cell surface glycoprotein CD4; CE: cornified envelope; CHK: cultured human keratinocytes; COX-2: cyclooxygenase-2; CYP: cytochrome P450; ERK/RSK2: extracellular signal-regulated protein/ ribosomal S6 kinase 2 kinase; FLI: Fos-like immunoreactive neurons; GSH-Px: glutathione peroxidase; GSK 3β: glycogen synthase kinase 3 beta; HaCaT: immortalized human keratinocytes cells; HeLa cells: a cell from a sample taken from a woman called Henrietta Lacks and was named using the two initials of her first (He) and last (La) names; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IgE: immunoglobulin E; $I_\kappa B$: ikappaB kinase; IKK: $I_\kappa B$α kinase; IL: interleukin; iNOS: inducible nitric oxide Synthase; JNK: c-Jun N-terminal kinase; MCP-1: monocyte chemotactic protein-1; mRNA: messenger RNA; NO: nitrogen oxide; N.S.: not stated; MCP: monocyte chemotactic protein; NF-$_\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NIK: NF-αB-inducing kinase; PARP: poly (ADP-ribose) polymerase; PGE_2: prostaglandin E2; PPAR: peroxisome proliferator-activated receptor; R-HepG2: human hepatoma cell line; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; THP1 human monocytic cell line; TNF-α: tumor necrosis factor-alpha; TSLP: thymic stromal lymphopoietin.

human solid tumor cell lines, § proteolytic form.

7.4.2 Experimental studies on *Rehmannia glutinosa* (Di huang)

In clinical Chinese Herbal Medicine, *Rehmannia glutinosa* has been divided into three forms according to how the root is prepared: *Xian di huang* (fresh root), *Sheng di huang* (dried root) and *Shu di huang* (steamed root). For the purpose of this discussion these are considered together. Common bioactive constituents purified from *Rehmannia glutinosa* include glycosides, glucide and amino acids with iridoid glycosides constituting the primary glycosides. Of the 32 compounds that have been isolated, the iridoid glycoside catalpol has the highest content (269).

Kim *et al* 1998 found that an aqueous extract of *Rehmannia glutinosa* steamed root (RGAE), dose-dependently reduced mortality in rats due to a compound 48/80-induced systemic allergic reaction and significantly inhibited the fatal shock (53.3%). Plasma histamine release induced by the compound was also significantly inhibited *in vivo*. In rats with a cutaneous allergic reaction induced by anti-dinitrophenyl IgE (anti-DNP IgE), RGAE inhibited passive cutaneous anaphylaxis (PCA) reactions in a dose-dependent manner. In an *in vitro* study of rat peritoneal mast cells (RPMC), the extract significantly inhibited histamine release induced by the compounds 48/80 and anti-dinitrophenyl (DNP) IgE, and dose-dependently inhibited TNF-α production induced by anti-DNP IgE. The authors indicated that the *Rehmannia glutinosa* extract exerted anti-inflammatory actions in these models of immediate type allergic reaction (270).

In an *in vitro* study by Baek *et al* 2012 on the anti-inflammatory effect of a water extract of *Rehmannia glutinosa* [*Saeng-jihwang* (SJH) in Korean, *aka* sheng di huang] in THP-1 cells, found that the extract decreased the production of intracellular reactive oxygen species (ROS) induced by Advanced Glycation End Products (AGEs) without change in the viability of the THP-1 cells. SJH dose-dependently degraded cytosolic $I_{\kappa}B$-α and reduced the nuclear localization of NF-$_{\kappa}$B p65. NF-$_{\kappa}$B mediates the gene expression of the pro-inflammatory mediators monocyte chemotactic protein-1 (MCP-1), RAGE [receptor for advanced glycation end products], inducible protein-10 (IP-10), iNOS, COX-2, and TNF-α. It suppressed the expression of TNF-α, COX-2, MCP-1 [monocyte chemotactic protein-1], IP-10 [Interferon gamma-induced protein 10] but had no effect on COX-1 [cyclooxygenase-1] which is not mediated by NF-$_{\kappa}$B. Pretreatment with SJH suppressed NO release induced by LPS (lipopolysaccharides). In addition, SJH down-regulated the

expression of RAGE and the mRNA expression of RAGE. These results indicated that SJH exerted an anti-inflammatory effect via reduction of NF-κB activity (271).

In an *in vitro* study on murine monocyte/macrophage RAW264.7 cells, a crude extract of *Rehmannia glutinosa* was assessed for anti-NO production, followed by fractionation to identify active components. The C3 sub-fraction suppressed NO production with about 100-fold greater potency than the crude extract. C3 also inhibited both the gene and protein expression of iNOS. In the LPS-stimulated macrophages, C3 down-regulated the main pro-inflammatory mediators/cytokines including PGE_2, IL-6 and COX-2. Furthermore, two compounds were purified from C3: rehmapicrogenin and cinnamic acid. The former exerted a significant inhibition on NO production but there was no inhibition from the latter. Therefore, rehmapicrogenin was partly responsible for the potent anti-inflammatory effect of C3. C3 appeared to act via iNOS gene and protein suppression, and blocking IL-6 and PGE_2 release. In summary, the C3 fraction showed a potent anti-inflammatory effect to which its derivative rehmapicrogenin partly contributed (272).

Wei and Ru 1997 conducted study to examine the effect of low-molecular-weight *Rehmannia glutinosa* polysaccharides (LRPS) on p53 gene expression in Lewis lung cancer cells using 3-groups: Saline group, LRPS group and Cyclophosphamide group (positive control). LRPS was found to inhibit the gene expression of p53 on Lewis lung cancer (273). Catalpol, along with other iridoid glycosides, has been shown to inhibit DNA polymerase (274) and has been the basis for the development of a number of derivatives that have been investigated as anti-proliferative agents (275, 276).

Table 7.3 Summary of experimental findings on the actions of *Rehmannia glutinosa* [adapted from Deng 2013 (135)]

Preparation, Active ingredients	**Study type, Model examined**	**Outcome / Pharmaceutical target**	**Regulating effect**	**Reference**
aqueous extract of *Rehmannia glutinosa* steamed root (RGAE), NS	*in vivo:* rat with compound 48/80-induced systemic allergic reaction	plasma histamine	down	Kim 1998 (270)
	in vivo: rat with anti-DNP IgE-induced cutaneous allergic reaction	passive cutaneous anaphylaxis reaction	inhibited	
	in vitro: rat peritoneal mast cells	histamine, TNF-α	down	
water extract, NS	*in vitro*: human monocytes (THP-1)	ROS, NF-$_{\kappa}$B (I_{κ}B-α, p65), MCP-1, RAGE, IP-10, iNOS, COX-2, TNF-α, protein-10, NO, mRNA COX-1	down no change	Baek 2012 (271)
aqueous extract sub-fraction C3, containing rehmapicrogenin & cinnamic acid	*in vitro*: lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages	NO, iNOS, PGE2, IL-6, COX-2	down	Liu 2012 (272)
low-molecular-weight *Rehmannia glutinosa* polysaccharides (LRPS)	*in vivo*: Lewis lung cancer model	p53	up	Wei 1997 (273)
compound 9a-b, molecular simplification of catalpol	*in vitro*: representative human solid tumor cell lines A2780 (ovarian), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast) & WiDr (colon)	50% growth inhibition (GI50),	active	Carcia 2010 (275)
	in vitro: HeLa & WiDr cells	annexin V binding	induce apoptosis	
compoud 9b, molecular	*in vitro*: HBL-100, SW1573 cells	cell cycle disturbances	cells arrested in	

simplification of catalpol			G0/G1	
	in vitro: HeLa cells	cyclin D1	reduced	
		cell cycle disturbances	cell cycle arrest on G1	
catapol	*in vivo*: *Tribolium castaneum* larvae	DNA Polymerase activity	inhibited	Pungitore 2004 (274)

α-SMA: α-smooth muscle actin; p21: Cyclin-dependent kinase inhibitor 1; p38: Activator of 90 kDa heat shock protein ATPase homolog 1; p53: Cellular tumor antigen; AIF: apoptosis-inducing factor; AP-1: activating protein-1; Bax protein: Bcl-2-associated X protein; Bcl-2 family proteins: B-cell lymphoma 2 family of apoptosis regulator proteins; CAT: catalase; CD: circular dichroism; $CD4^+$ T cells: T-cell surface glycoprotein CD4; CE: cornified envelope; CHK: cultured human keratinocytes; COX-2: cyclooxygenase-2; CYP: cytochrome P450; ERK/RSK2: extracellular signal-regulated protein/ ribosomal S6 kinase 2 kinase; FLI: Fos-like immunoreactive neurons; GSH-Px: glutathione peroxidase; GSK 3β: glycogen synthase kinase 3 beta; HaCaT: immortalized human keratinocytes cells; HeLa cells: a cell from a sample taken from a woman called Henrietta Lacks and was named using the two initials of her first (He) and last (La) names; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IgE: immunoglobulin E; $I_\kappa B$: ikappaB kinase; IKK: $I_\kappa B\alpha$ kinase; IL: interleukin; iNOS: inducible nitric oxide Synthase; JNK: c-Jun N-terminal kinase; MCP-1: monocyte chemotactic protein-1; mRNA: messenger RNA; NO: nitrogen oxide; N.S.: not stated; MCP: monocyte chemotactic protein; NF-$_\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NIK: NF-αB-inducing kinase; PARP: poly (ADP-ribose) polymerase; PGE_2: prostaglandin E2; PPAR: peroxisome proliferator-activated receptor; R-HepG2: human hepatoma cell line; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; THP1 human monocytic cell line; TNF-α: tumor necrosis factor-alpha; TSLP: thymic stromal lymphopoietin.

human solid tumor cell lines, § proteolytic form.

7.4.3 Experimental studies on *Salvia miltiorrhiza* (Dan shen)

The main lipid-soluble compounds of *Salvia miltiorrhiza* includes tanshinone (I, IIA, IIB), iso-tanshinone (I, II), cryptotanshinone and dihydrotanshinone I, and the water-soluble compounds include salvianic acid A, salvianolic acid B and rosmarinic acid. This herb and its constituent tanshinones have received much research attention for their cardiovascular effects and have been developed into a number of commercial preparations (277-281).

Parajuli *et al* 2013 evaluated the effects of a standardised fraction of *S. miltiorrhiza* (PF2401-SF) on apoptosis and proliferation using in hepatic stellate cells (HSC) and in carbon tetrachloride (CCl_4) induced injury in rats. PF2401-SF dose-dependently reduced the viability of t-HSC/Cl-6 cells and dose-dependently improved the protease activity of caspase 3, time-dependently activated apoptosis flags (i.e., procaspase 3 and PARP), and dose-dependently activated upstream caspase 8 and 9 and their accompanied cleavage. In addition, PF2401-SF time-dependently improved pro-apoptotic Bax protein [Bcl-2-associated X protein] and suppressed anti-apoptotic Bcl2 [B-cell lymphoma 2 family of apoptosis regulator proteins]. These results showed a caspase-dependent pathway for PF2401-SF-regulated apoptosis in t-HSC/Cl-6 cells. In the *in vivo* study of subacute CCl_4 induced liver injury in a rat model, the extract remarkably reduced the expression of α-smooth muscle actin (α-SMA) and increased the amount of TdT mediated UTP Nick-End Labelling (TUNEL) positive cells, which indicated that PF2401-SF inhibited HSC cells by up-regulating apoptosis *in vivo* (282).

Li FL *et al* 2012 investigated the effects of tanshinone IIA (Tan IIA) isolated from *Salvia miltiorrhiza* on the inhibition of the growth of mouse keratinocytes *in vitro*. Tan IIA dose- and time-dependently inhibited the growth of keratinocytes at IC_{50} values: 4.33±1.35, 1.89±0.65, and 1.14±0.87 μg/mL, when incubated for 24, 48, and 72 hours, respectively. It also dose-dependently inhibited colony number growth curves. Apoptotic cells treated with Tan IIA gradually increased in a dose dependent manner, which presented about a 25-fold growth at the highest concentration. Subsequently, the number of DNA strand breaks was remarkably higher in the Tan IIA-treated groups compared with the control group. Caspase-3 and PARP treated with Tan IIA were increased in a dose dependent manner whereas Ac-DEVD-CHO, a caspase-3 specific inhibitor, reduced the apoptosis. Thus Tan IIA inhibited the growth of keratinocytes via a caspase-dependent apoptotic pathway. Tan

IIA concentration- and time-dependently decreased mitochondrial membrane potential as well as increased cytochrome c content. In a time-dependent manner, Tan IIA increased S and G2/M phase cells whereas it decreased G1 phase cells. Specifically, it down-regulated cyclin A and pCDK2 [phospho-Cyclin-dependent kinase 2], which relate to the S phase of the cell cycle, and down-regulated expression of PCNA [Proliferating Cell Nuclear Antigen] which is involved in cell proliferation. Therefore, Tan IIA suppressed the keratinocytes via cell cycle arrest (283).

In murine hepatoma H22 cells, Tanshinone IIA Microemulsion (Tan IIA ME) resulted in broken and necrotic cells at 0.5 μM and 2 μM TanIIA ME for 48 hours. In H22 tumor-bearing mice, the tumor inhibition rate reached 34.68% (dosage: 4mg/kg) or 47.17% (dosage: 8mg/kg) compared with 63.06% for 5-FU (25 mg/kg). *In vitro* and *in vivo*, TanIIA ME down-regulated Bcl-2, and up-regulated Bax and caspase-3 to induce apoptosis of hepatocellular carcinoma cells (284).

In hepatocellular carcinoma H22 cells, a polysaccharide derived from *Salvia miltiorrhiza* (SMP-W1) showed its *in vitro* immunoregulatory and anti-proliferative properties. SMP-W1 dose-dependently inhibited cell viability with significant cytotoxicity to H22 cells. After 48 hours of treatment with concentrations of 200 and 400 μg/ml, the inhibition rate on H22 cells exceeded 43%. In the H22 bearing mice, SMP-W1 dose-dependently reduced the tumour weight after 10 days treatment. The highest tumour inhibitory rate of 55.1% was for 200 mg/kg of SMP-W1 which was close to the 60.5% achieved by the 5-FU positive control. For body weight, spleen and thymus indexes, the 5-FU positive control was significantly worse than the positive control whereas the SMP-W1 groups showed improvements over the positive and negative controls. The SMP-W1 groups also showed improvements over the control groups for appetite, activity and coat lustre. This implied there were no adverse effects of the SMP-W1 on body weight or immune organs. SMP-W1 significantly stimulated the secretion of TNF-α as well as anti-oxidant enzymes (SOD [superoxide dismutase], CAT [catalase] and GSH-Px [glutathione peroxidase]) in a dose-dependent manner. These experiments demonstrated SMP-W1 exerted anti-proliferative and immuno-regulatory effects (285).

S. miltiorrhiza lipid-soluble extracts (SMLE) were reported to exert anti-inflammation effects both *in vitro* and *in vivo*. In lipopolysaccharide (LPS)-stimulated murine macrophage RAW 264.7 cells, SMLE dose- and time-dependently inhibited NO production without

cytotoxicity with an IC_{50} of 2.29 mg/mL. It dose-dependently inhibited the mRNA [messenger RNA] and protein expression of iNOS, pro-inflammatory cytokine levels (TNF-α, IL-1b and IL-6), and intracellular ROS (reactive oxygen species). It also significantly inhibited $I_{\kappa}B$-α degradation, NF-$_{k}$B translocation (p65), and CD14 [cluster of differentiation 14] expression. Intracellular GSH [intracellular glutathione] was prevented from loss by the extract but it had little impact on TLR4 [Toll-like receptor 4]. Therefore, SMLE suppressed inflammation through NF-$_{\kappa}$B regulation in RAW 264.7 cells. In mice with lethal endotoxemia induced by LPS, the survival rate was reversed from 50% for LPS (25 mg/kg i.p.) to 70% for SMLE (10 mg/kg i.p.) and 90% for SMLE (40 mg/kg i.p.). In a cecal ligation and puncture (CLP)-induced sepsis model, survival was increased from 16% for CLP alone to 50% with SMLE (40 mg/kg i.p.) treatment. SMLE also significantly suppressed the serum TNF-α production induced by LPS. In a PMA-induced ear edema model, SMLE significantly inhibited edema when used topically but not when used orally. This experiment showed that SMLE induced anti-inflammatory effects *in vitro* and *in vivo* and had a protective effect on endotoxemia and sepsis *in vivo* (286).

Jang *et al* 2006 found that the addition of tanshinone IIA to murine macrophages (RAW 264.7) treatment with lipopolysaccharide (LPS) inhibited inflammatory response via reducing the production of pro-inflammatory mediators. It inhibited NF-$_{\kappa}$B (p65), the MAPKs p38 [Activator of 90 kDa heat shock protein ATPase homolog 1], ERK1/2 and JNK, as well as NIK [NF-$_{\kappa}$B-inducing kinase] and IKKα/β [IκBα kinase α/β] (Table 7.4) (287).

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Table 7.4 Summary of experimental findings on the actions of *Salvia miltiorrhiza* [adapted from Deng 2013 (135)]

Preparation, Active ingredients	**Study type, Model examined**	**Outcome / Pharmaceutical target**	**Regulating effect**	**Reference**
tanshinone IIA	*in vitro:* lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages	NF-$_{\kappa}$B (p65), p38, ERK1/2, JNK, NIK & IKKα/β	down	Jang 2006 (287)
extract, PF2401-SF (Standardized Fraction of *S. miltiorrhiza*)	*in vitro*: hepatic stellate (t-HSC/Cl-6) cells	caspase 3, 8 & 9, PARP, Bax protein Bcl-2 protein	up down	Parajuli 2013 (282)
	in vivo: male Sprague-Dawley rats with CCl_4 induced subacute liver injury	α-SMA TUNEL-positive cells	reduced no. increased	
tanshinone IIA	*in vitro*: primary mouse keratinocytes	growth (MTS/PMS) caspase-3, PARP cyclin A, pCDK2	retardation up down	Li FL 2012 (288)
tanshinone IIA (micro emulsion)	*in vitro*: murine hepatoma H22 cells;	Bcl-2 Bax, caspase-3	down up	Ma 2013 (284)
	in vivo: Balb/c mice bearing tumor H22	tumor weight	reduced	
polysaccharide (SMP-W1) fraction	*in vitro*: hepatocellular carcinoma H22 cells	proliferation	inhibited	Liu 2013 (285)
	in vivo: male Balb/c mice bearing hepatoma H22	tumor growth TNF-α	reduced up	
S. miltiorrhiza lipid-soluble extract (SMLE)	*in vitro*: lipopolysaccharide (LPS)-stimulated murine macrophage RAW 264.7 cells	NO, iNOS, IL-1b, IL-6, p65, NF-$_{k}$B I$_{\kappa}$B-α TNF-α	down up down	Li M 2012 (286)
	in vivo: Balb/c mice with: 1. lethal endotoxemia & sepsis; 2. ear-edema	1. mortality; 2. oedema	1. reduced, 2. reduced (topical use)	

α-SMA: α-smooth muscle actin; p21: Cyclin-dependent kinase inhibitor 1; p38: Activator of 90 kDa heat shock protein ATPase homolog 1; p53: Cellular tumor antigen; AIF: apoptosis-inducing factor; AP-1: activating protein-1; Bax protein: Bcl-2-associated X protein; Bcl-2 family proteins: B-cell lymphoma 2 family of

apoptosis regulator proteins; CAT: catalase; CD: circular dichroism; $CD4^+$ T cells: T-cell surface glycoprotein CD4; CE: cornified envelope; CHK: cultured human keratinocytes; COX-2: cyclooxygenase-2; CYP: cytochrome P450; ERK/RSK2: extracellular signal-regulated protein/ ribosomal S6 kinase 2 kinase; FLI: Fos-like immunoreactive neurons; GSH-Px: glutathione peroxidase; GSK 3β: glycogen synthase kinase 3 beta; HaCaT: immortalized human keratinocytes cells; HeLa cells: a cell from a sample taken from a woman called Henrietta Lacks and was named using the two initials of her first (He) and last (La) names; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IgE: immunoglobulin E; $I_\kappa B$: ikappaB kinase; IKK: $I_\kappa B\alpha$ kinase; IL: interleukin; iNOS: inducible nitric oxide Synthase; JNK: c-Jun N-terminal kinase; MCP-1: monocyte chemotactic protein-1; mRNA: messenger RNA; NO: nitrogen oxide; N.S.: not stated; MCP: monocyte chemotactic protein; NF-$_\kappa$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NIK: NF-αB-inducing kinase; PARP: poly (ADP-ribose) polymerase; PGE_2: prostaglandin E2; PPAR: peroxisome proliferator-activated receptor; R-HepG2: human hepatoma cell line; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; THP1 human monocytic cell line; TNF-α: tumor necrosis factor-alpha; TSLP: thymic stromal lymphopoietin.

human solid tumor cell lines, § proteolytic form.

Anti-psoriatic actions of the main herbs identified in SR2: single herbs used topically for psoriasis (7.4.4-7.4.7)

Four herbs, *Aloe vera*, *Indigo naturalis*, *Camptotheca acuminate* and *Mahonia aquifolium* were frequently used topically as single herbs in the management of psoriasis. Each showed effectiveness and had satisfactory safety.

7.4.4 Experimental studies on *Aloe vera* (Lu hui)

Aloe vera has been widely used in a variety of dermatological conditions (41). *Aloe vera* applied topically, administered intraperitoneally or in combination modulated the inflammatory response in a salmonella OmpR [outer-membrane proteins] mediated inflammation model in mice (289). A study of wound healing in rats found that the topical application of a gel of *Aloe vera* mucilage applied for 14 days to surgically induced wounds produced greater tensile strength compared with silver sulfadizine cream (290). In a study of skin lesions in military personnel exposed to mustard gas, an *Aloe vera*/olive oil cream showed similar efficacy to betamethasone cream for pruritus, scaling and dry skin and was superior for fissure and excoriation (291). However a review of RCTs of *Aloe vera* products for wound healing was inconclusive (292).

In the mouse tail model of psoriasis, Dhanabal *et al* tested the anti-psoriatic effects of an ethanolic extract of *Aloe vera* gel and reported effects similar to those of tazarotene (0.1%) (293). In a *Croton tiglium* oil skin carcinogenesis model in mice, Saini *et al* found that the topical application of *Aloe vera* extract as well as oral *Aloe vera*, reduced the number of papillomas (294). In human non-melanoma cancer cells, aloe emodin induced apoptosis by activating caspase-8, -9 and -3 expression (295).

7.4.5 Experimental studies on *Indigo naturalis* (Qing dai)

Indigo naturalis is derived from the stems and leaves of herbs described as *Da qing ye* and *Ban lan gen*, which may originate from the plants *Isatis tinctoria, Baphicacanthus cusia, Polygonum tinctorium*, *Strobilanthes formosanus* and *Indigofera tinctoria* (296, 297). These plants contain similar compounds and *Qingdai* (*Indigo naturalis*) reportedly contains indigotin, indirubin, isatin, nonacosane, tryptanthrin and qingdainone (297-299).

Indirubin extracted from *Polygonum tinctorium* was found to effectively control

2,4,6-trinitro-l-chlorobenzene (TNCB)-elicited mouse ear swelling and the indirubin inhibited interferon-γ in the supernatants of mouse lymphocytes induced by the model (300). In an *in vivo* study of acute inflammation (xylene-induced ear edema in mice), *Indigo naturalis* showed a potent anti-inflammatory efficacy using both external and internal administration. However, for sub-acute inflammation (cotton ball-induced granuloma in mice), it only presented a remarkable anti-inflammatory effect when used externally rather than internally. This study implied that the anti-inflammatory effects of *Indigo naturalis* were superior when it was applied topically (301).

As cyclin-dependent kinases (CDKs) stimulate and regulate the cell cycle, compounds that can inhibit CDKs have been a focus in the control of proliferative diseases such as cancer and psoriasis. Suzuki *et al* indicated that indirubin could improve the differentiation of human HL-60 cells by inhibiting CDK2 and activating transcription factor PU.1 (302).

In Moon 2006, analogs and derivatives of *indirubin* showed high anti-proliferative effects in a cyclin-dependent kinase CDK2 enzyme assay (303). In addition, Lee *et al* reported that a novel CDK inhibitor, indirubin-5-nitro-30-monoxime, had a promising inhibitory effect in cell cycle progression and apoptosis of human lung cancer cells A549 (304).

7.4.6 Experimental studies on *Camptotheca acuminata* (Xi shu)

Camptothecin (CPT) can be derived from *Camptotheca acuminata* and *Nothapodytes foetida* (305). CPT has been developed into the anti-cancer agents irinotecan and topotecan (306). *Camptotheca* extracts and camptothecin have been used as anti-psoriatic therapies in China for decades based on experimental and clinical studies that demonstrated the anti-psoriatic effects of topical preparations (307, 308).

Lin and Huang conducted a series of experiments on the anti-proliferative effects of CPT in mice and human keratinocytes. In mouse vaginal epithelial cells, CPT inhibited proliferation at 10^{-7}-10^{-9} mol/L. In mouse tail scale epidermis, CPT promoted differentiation at 10^{-9}-10^{-11} mol/L. CPT also showed proliferation-inhibiting and differentiation-improving effects in human keratinocytes. This was related to DNA topoisomerase, which is important in psoriasis with its function-inducing and differentiating effects (309, 310).

CPT was found to inhibit the proliferation of HaCaT cells in a time and

concentration-dependent manner, and induce apoptosis in a concentration-dependent manner resulting in cell-cycle arrest in the S stage. CPT inhibited telomerase activity even at concentrations insufficient to induce apoptosis (311). Although much of the research into CPT derivatives has focused on cancer, some such as isocamptothecin show promise for psoraisis (312).

7.4.7 Experimental studies on *Mahonia aquifolium* (Gong lao mu)

In vitro studies of *Mahonia aquifolium,* including its extracts, have found anti-proliferative (313), anti-mutagenic (314), and anti-oxidant (315) effects; inhibition of interleukin-8 production (316), and activity against micro-organisms (314, 317). Similarly, anti-inflammatory (318, 319), anti-oxidant (318-320) and anti-proliferative effects (320, 321) have been reported for other *Mahonia* species.

Berberine, which is found in various *Mahonia*, *Berberis* and *Coptis* species (322-325), has received considerable research attention. It has demonstrated dose-dependent anti-inflammatory effects and improved insulin resistance *in vitro* (323). Some other compounds isolated from *Mahonia*, such as jatrorrhizine, magnoflorine, baluchistine, and aromoline, have also received the research attention (314-316).

In a study using the human monocytic cell-line THP-1, a crude hydroalcoholic extract of *Mahonia aquifolium* stem bark showed a partially inhibitory effect on IL-8 [intereukin 8] production after 2-days administration. However, a polysaccharide isolated from this extract, greatly elevated IL-8 production after 24/48-hours. This demonstrated the complex biological activity of the extract. The inhibitory effects may have resulted from the alkaloids in the extract while the polysaccharide may have increased B-lymphocyte proliferation and stimulated the immune system or stimulated cytokine production (326).

Psoriasis is thought to be an inflammatory disorder involving T-cells. Psoriatic lesions result from $CD4^+$ T cells adhering to endothelial cells and subsequently moving to skin tissue. In endothelial cells, the combination of antilymphocyte function-associated antigen type 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) most effectively inhibited adhesion induced by TNF-alpha or peripheral blood mononuclear cells (PBMC) from psoriasis patients (327). In the RCT of *Mahonia* by Augustin *et al* 1999, biopsies from

patients that measured ICAM-1, its keratinocyte expression was found to be significantly inhibited along with a mild reduction in its endothelium expression (328).

Mahonia extracts were reported to exert antimutagenic/anticarcinogenic activity in acridine orange (AO)-induced chloroplast mutagenesis in *Euglena gracilis*. Within the protoberberine alkaloid fractions, berberine and jatrorrhizine showed significant concentration-dependent inhibition (314).

Besides the clinical studies of *Mahonia*, it is notable that in SR4 the clinical study by Wang *et al*. (243) included *Phellodendron amurense* bark while the trial by Liu *et al*. (240) contained *Coptis chinensis* root, both of which contain berberine (297, 329).

Anti-psoriatic actions of the main herbs identified in SR3: external herbal formulae for psoriasis (7.4.8-7.4.9)

To further explore the possible effects of the individual HMs used in multi-ingredient topical formulae in multiple studies, evidence derived from experimental studies of the actions of *Sophora flavescens* and *Lithospermum erythrorhizon* that are relevant to psoriasis were reviewed. These are summarised in Tables 7.5-7.6.

7.4.8 Experimental studies on *Sophora flavescens* (Ku shen)

S. flavescens contains more than 20 alkaloids including matrine and oxymatrine, and a number of flavonoids (330, 331).

In an *in vivo* study, Kim *et al* 2012 used a 1-fluoro-2, 4-dinitrofluorobenzene (DNFB)-induced contact dermatitis mouse model to assess the effects of an extract of *S. flavescens* root. They reported that the topical application of the *S. flavescens* root extract inhibited ear swelling induced by DNFB and reduced the following histopathological changes: hyperplasia, edema and spongiosis. The *S. flavescens* root extract suppressed DNFB-induced increases in the levels of IFN-γ and TNF-α. In a cell-line study using RBL-2H3 cells, the same group reported that the *S. flavescens* root extract (<100 mg/mL) dose-dependently inhibited migration rates of RBL-2H3 cells at concentrations of up to 100 μg/mL. They also conducted assays of β-hexosaminidase and histamine release, which showed that pre-treatment with the *S. flavescens* root extract reduced the release of β-hexosaminidase and histamine (> 50 μg/mL) in a dose-dependent manner. The authors

argued that these anti-inflammatory actions of the *S. flavescens* root extract involved the Th1 skewing reaction and inhibition of mast cell degranulation (332).

Liu *et al* 2007 conducted a study of human epidermal keratinocytes (HaCaT cells) and dermal fibroblasts which found that matrine suppressed the up-regulation of neurokinin-1 receptor (NK-1R) expression induced by substance P (SP). Matrine also modulated the production of cytokines and chemokines in both cell lines. In the presence of SP, matrine down-regulated the production of IL-1β, IL-8 and MCP-1, and it up-regulated IFN-γ, but matrine had no effect on the secretion of IL-6. These results demonstrated that matrine exerted anti-inflammatory actions that are relevant to psoriasis and to other disorders characterised by chronic inflammation of the skin (333).

An *in vivo* study in mice by Liao et al found that the intramuscular administration of oxymatrine controlled exudative inflammation and an *in vitro* study found that oxymatrine can exert a higher stabilizing effect on the red blood cell (RBC) surface compared with analgin, and it inhibited the heat denaturation of protein (334).

Zheng *et al*. 2005 reported that the alkaloid oxymatrine reduced inflammatory symptoms and histological damage in a colitis model in rats (335). Jin *et al* 2010 investigated an alkaloid-free prenylated flavonoid-enriched fraction (PFS) from *S. flavescens* root and reported that it showed anti-inflammatory activity *in vitro* and it reduced arthritic inflammation in a rat arthritis model in a dose-dependent manner. In an acetic acid-induced writhing model, the PFS demonstrated a potent analgesic effect (336). An *in vitro* study by Zhou *et al* 2009 found that the pterocarpan flavonoid, trifolirhizin, which was extracted from *S. flavescens* roots showed anti-inflammatory effects in lipopolysaccharide (LPS)-stimulated mouse J774A.1 macrophages by reducing the expression of TNF-α and IL-6 and by inhibiting COX-2 expression. In human A2780 ovarian and H23 lung cancer cells, trifolirhizin showed anti-proliferative actions (234).

Burghe *et al* 2011 investigated the effects of kurarinone, a flavanone isolated from *S. flavescens*, in three cancer cell-lines: estrogen-unresponsive fibroblasts, ribosomal S6 kinase 2 kinase (RSK2) knockout cells, and estrogen receptor (ER)-deficient breast tumour cells. They reported that kurarinone could suppress NF-$_{\kappa}$B driven IL-6 and cyclin D1 expression and it inhibited tumour cell proliferation (337). Liu *et al* 2008 investigated a lectin derived from *S. flavescens* in human HeLa cells. They reported that it time- and dose-dependently

induced apoptosis in the human HeLa cells and that the mechanism involved caspases 3, 8, 9, and 10 and pancaspace. The lectin appeared to bind to mannose branches on the cell surface and this led to the caspase cascade (338).

Table 7.5 Summary of experimental findings on the actions of *Sophora flavescens* [adapted from Deng 2013 (158)]

Preparation	**Active ingredients**	**Study category**	**Outcome / Pharmaceutical target**	**Regulating effect**	**Reference**
compound	matrine	*in vitro*	NK-1R, IL-1β, IL-8, TNF-α, MCP-1	down	Liu 2007
		in vitro	IFN-γ	up	
		in vitro	IL-6	none	
extract	NS	*in vivo*	IFN-γ, TNF-α	down	Kim 2012
		in vitro	β-hexosaminidase and histamine	down	
compound	oxymatrine	*in vivo*	TNF-α, IL-6, NF-$_{\kappa}$B, ICAM-1	down	Zheng 2005
compound	PFS	*in vitro*	COX-2, iNOS, TNF-α, IL-6, PGE_2, NO	down	Jin 2010
compound	trifolirhizin	*in vitro*	TNF-α, IL-6, COX-2	down	Zhou 2009
			human A2780 ovarian cells & H23 lung cancer cells	reduced proliferation	
compound	mannose-binding lectin	*in vitro*	HeLa cells	induced apoptosis	Liu 2008
		in vitro	caspase 3,8,9,10, pancaspace	up	
		in vitro	mannose-containing receptor	up	
compound	kurarinone	*in vitro*	NF-$_{\kappa}$B	down	Berghe 2011
			ERK/RSK2 pathways	inhibited	

AP-1: activating protein-1; Bax protein: Bcl-2-associated X protein; Bcl-2 family proteins: B-cell lymphoma 2 family of apoptosis regulator proteins; CD: circular dichroism; CD4+ T cells: T-cell surface glycoprotein CD4; CHK: cultured human keratinocytes; COX-2: cyclooxygenase-2; ERK/RSK2: extracellular signal-regulated protein/ ribosomal S6 kinase 2; HeLa cells: a cell from a sample taken from a woman called Henrietta

Lacks and was named using the two initials of her first (He) and last (La) names; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IgE: immunoglobulin E; $I_{\kappa}B$: I kappa B kinase; IL: interleukin; iNOS: inducible nitric oxide synthase; mRNA: messenger RNA; NO: nitric oxide; N.S.: not stated; MCP: monocyte chemotactic protein; NF-$_{\kappa}$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NK-1R: neurokinin-1 receptor; PCNA: proliferating cell nuclear antigen; PFS: prenylated flavonoid-enriched fraction; PGE_2: prostaglandin E2; SPT: serine palmitoyl transferase; TNF-α: tumour necrosis factor-alpha.

7.4.9 Experimental studies on *Lithospermum erythrorhizon* (Zi cao)

The herb *zi cao* is mainly derived from *Lithospermum* species particularly *L. erythrorhizon.* It contains various chemical constituents such as shikonin derivatives, phenolic and quinonic compounds, alkaloids, phenolic acids, triterpenes, acidic polysaccarides, and flavonoids. The herb is also derived from *Arnebia euchroma* which contains shikonin and related compounds. Of the compounds contained in these species, shikonin and its derivatives have shown the most promising pharmaceutical actions (339).

Studies of *L. erythrorhizon* root extracts and its active constituents have found anti-proliferative and anti-inflammatory effects in cell-lines and animal models. Rajasekar *et al* 2012 investigated the effects of a root extract that contained shikonin and its derivatives in B16F10 melanoma cells and reported that the extract dose-dependently inhibited cell growth. In addition, the extract dose-dependently increased the percentage of sub-G1 phase cells, which reduced anti-apoptotic Bcl-2 family proteins and improved apoptotic Bax protein expression. *In vivo*, in a C57BL/6 mouse model the extract reduced the tumour size (A) and weight (B), and the corresponding tumor volume (calculated as $V= AB^2/2$) in a concentration dependent manner by increasing necrotic cells (340).

In murine vascular smooth muscle cells, Zhang *et al* 2005 reported that shikonin did not demonstrate cytotoxic effect but it time- and dose-dependently inhibited proliferation by promoting apoptosis and blocking cell cycle progression (341). In breast tumour cells, shikonin inhibited the proliferation by down-regulating the expression of steroid sulfatase genes (342). Yoon *et al* 1999 investigated shikonin in the HL60 human premyelocytic leukemia cell line and reported that shikonin inhibited proliferation via the activation of caspase-3 to induce apoptosis (343). In an *in vivo* study, Hisa *et al* 1998 found that shikonin inhibited TNF-α and B16 melanoma-induced murine angiogenesis. In addition, shikonin inhibited proliferation, movement and network formation in endothelial cells on Matrigel via suppression of integrin α V β3 expression (344). In an acute murine ear oedema model the addition of topical shikonin dose-dependently reduced ear oedema by blocking the activation of $I_\kappa B$-α and thereby suppressing the activation of NF-$_\kappa$B (345).

In a lipopolysaccharide (LPS)-induced inflammation model in mouse macrophage cells, Han *et al* 2008 reported that *L. erythrorhizon* extracts dose-dependently decreased the levels of

IFN-γ, TNF-α, IL-6, iNOS and IL-1β mRNA and suppressed the activation of AP-1 and NF-$_\kappa$B via suppression of $I_\kappa B\alpha$ degradation. They also reported that *L. erythrorhizon* inhibited both c-Jun N-terminal kinase (JNKs) and extracellular signal-regulated signalling pathways (346).

Kim *et al* 2007 conducted a series of experiments on *L. erythrorhizon* root extract. In an *in vivo* study of passive cutaneous anaphylaxis (PCA) induced by DNP-HAS injection in rats, they reported that prior oral administration of *L. erythrorhizon* root extract significantly inhibited PCA reaction. In a study of murine peritoneal mast cells, the *L. erythrorhizon* dose-dependently reduced compound 48/80-induced histamine release. In human mast cells (HMC-1), the *L. erythrorhizon* extract demonstrated no cytotoxic effects and it reduced the production of the inflammatory cytokines IL-6, IL-8, TNF-α. In addition, the extract inhibited the activation of the pro-inflammatory cytokine NF-$_\kappa$B by supressing $I_\kappa B$-α degradation (347).

L. erythrorhizon extracts have shown efficacy in animal models of dermatological disorders. In an oxazolone-induced murine atopic dermatitis model, Lee *et al* 2009 reported that *L. erythrorhizon* extracts alleviated erythema, scaling and excoriation compared to control. There was reduction in serum IgE and Western blotting demonstrated inhibition of COX-2 and iNOS, and attenuation of $I_k B\alpha$ (348). In guinea pigs with epidermal hyperproliferation induced by an essential fatty acid deficient diet, Kim *et al* 2006 reported that oral dietary supplementation with *L. erythrorhizon* extract effectively controlled the epidermal hyperproliferation (349). In a murine model of atopic dermatitis, an *L. erythrorhizon* root extract was administered to NC/Nga mice. Subsequently, scratching behaviour was found to reduce in the experimental group. This was associated with lower serum IgE levels and an increase in epidermal ceramide level due to a reduction in ceramide degradation (350).

L. erythrorhizon extracts and shikonin have been reported to have skin protective effects and improve tissue repair. Ishida *et al* 2007 reported that the addition of a *L. erythrorhizon* extract to normal human epidermal keratinocytes (NHEK) that were irradiated by UVB, resulted in improved cell viability, and decreased the levels of IL-1β, IL-6, IL-8, and TNF-α. The extract dose-dependently inhibited caspase-3 activation and reduced the up-regulation of P53 expression. The authors concluded that the extract, which included shikonin and related compounds, may provide photoprotection for the skin (351).

In a wound healing model in rats, Ozaki *et al* 1998 found that both shikonin and alkannin dose-dependently enhanced the proliferation of granulation tissue. This was via increase in the number of $CD11b^+$ cells in granulation tissue and accelerated proliferation of fibroblasts and collagen (352). In a wound scratch model of cultured human keratinocytes (CHK) and dermal fibroblasts, Kim *et al* 2012 reported that an aqueous extract of *L. erythrorhizon* promoted wound-healing at low-doses by promoting the movement, but not the proliferation, of both cell types and by accelerating lipid synthesis (353).

Table 7.6 Summary of experimental findings on the actions of *Lithospermum erythrorhizon* [adapted from Deng 2013 (158)]

Preparation	**Chemical constituents**	**Study type**	**Target**	**Regulating effect**	**Reference**
extract	Contained shikonin & its derivatives	*in vitro*	B16F10 melanoma cells caspase 3	induced apoptosis up	Rajasekar 2012
		in vitro	Bcl-2 family proteins	down	
		in vitro	Bax protein	up	
		in vivo	necrotic cells	up	
compound	shikonin	*in vitro*	MCF-7 and SK-BR-3 cells	reduced proliferation	Zhang 2009
			STS mRNA & enzyme activity	down	
compound	shikonin	*in vitro*	HL60 human leukemia cells caspase-3	induced apoptosis up	Yoon 1999
compound	shikonin	*in vitro*	$p21^{wif1/cipl}$	up	Zhang 2005
		in vitro	cyclin D_1, E, PCNA	down	
		in vitro	$p27^{kipl}$, p53	none	
extract	N.S.	*in vivo*	ceramide	up	Kim 2006
extract	N.S.	*in vivo*	IgE, protein expression of SPT & ceramidase, mRNA expression of	down	Kim 2009

			ceramidase		
			ceramide	up	
extract	N.S.	*in vitro*	histamine	down	Kim 2007
		in vitro	IL-6, IL-8, TNF-α, NF-$_{\kappa}$B	down	
		in vitro	I$_{\kappa}$B-α	up	
extract	N.S.	*in vivo*	IgE, I$_{\kappa}$B-α, COX-2, iNOS,	down	Lee 2009
extract	N.S.	*in vitro*	IFN-γ, IFN-α, IL-6, IL-1β, iNOS, AP-1, NF-$_{k}$B	down	Han 2008
extract	N.S.	*in vitro*	COX-1, COX-2	down	Kawata 2008
extract	Contained shikonin, β – Hydroxyisovalerylshikonin, Acetylshikonin, Isobutyrylshikonin, β, β – Dimethylacrylshikonin, α -Methyl-n-butyrylshikonin, Isovalerylshikonin	*in vitro*	IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF-α, caspase-3, p53	down	Ishida 2007
compound	shikonin	*in vivo*	I$_{\kappa}$B-α, NF-$_{\kappa}$B	down	Andújar 2010
compound	shikonin	*in vivo*	TNF-α & B16 melanoma-induced angiogenesis	down	Hisa 1998
		in vitro	integrin α V β3	down	
extract	N.S.	*in vitro*	lipid, CHK, dermal fibroblasts	up	Kim 2012
compound	shikonin & alkannin	*in vivo*	CD11b^{+} cells	increased no.	Ozaki 1998

			fibroblasts & collagen fibre	accelerated proliferation	

AP-1: activating protein-1; Bax protein: Bcl-2-associated X protein; Bcl-2 family proteins: B-cell lymphoma 2 family of apoptosis regulator proteins; CD: circular dichroism; CD4+ T cells: T-cell surface glycoprotein CD4; CHK: cultured human keratinocytes; COX-2: cyclooxygenase-2; ERK/RSK2: extracellular signal-regulated protein/ ribosomal S6 kinase 2; HeLa cells: a cell from a sample taken from a woman called Henrietta Lacks and was named using the two initials of her first (He) and last (La) names; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IgE: immunoglobulin E; $I_{\kappa}B$: I kappa B kinase; IL: interleukin; iNOS: inducible nitric oxide synthase; mRNA: messenger RNA; NO: nitric oxide; N.S.: not stated; MCP: monocyte chemotactic protein; NF-$_{\kappa}$B: nuclear factor kappa-light-chain-enhancer of activated B cells; NK-1R: neurokinin-1 receptor; PCNA: proliferating cell nuclear antigen; PFS: prenylated flavonoid-enriched fraction; PGE_2: prostaglandin E2; SPT: serine palmitoyl transferase; TNF-α: tumour necrosis factor-alpha.

Anti-psoriatic actions of the main herbs identified in SR4: external herbs combined with APP for psoriasis (7.4.10-7.4.12)

In this SR of combination therapies, the main herbs used topically were *Sophora flavescens*, *Cnidium monnieri, Dictamnus dasycarpus* and borneol. The effects of *S. flavescens* have been discussed earlier (see 7.4.8).

7.4.10 Experimental studies on *Cnidium monnieri*

The main bioactive ingredients of *Cnidium monnieri* seeds are coumarins, with osthole (*aka* osthol) having the highest concentration (354, 355). Liao *et al*. 2010 assessed the effects of osthole and four other coumarins isolated from *Cnidium* in murine macrophages. They reported that osthole was an antioxidant and it had the most pronounced anti-inflammatory effects of the five compounds investigated (355). Tse *et al* 2006 reported that a *Cnidium* extract had an anti-proliferative effect on cultured HaCaT human epidermal keratinocytes (356). In addition, osthole has demonstrated anti-proliferative effects in many cell line studies (357).

An *in vivo* study of extracts of *Sophora* and *Cnidium* in a serotonin-induced itching model in mice reported that both extracts exerted potent antipruritic effects. Besides, they found that the effect of *Sophora* was superior to that of *Cnidium*, was dosage-dependent and it did not inhibit locomotor activity (358).

7.4.11 Experimental studies on *Dictamnus dasycarpus*

The root-bark of *Dictamnus dasycarpus* includes around 11 alkaloids, 16 triterpenoids and 16 sesquiterpenoids (359). The limonoid triterpenoid, fraxinellone, and the sesquiterpenoid, dictamnoside A are constituents of the root-bark of *D. dasycarpus*. Each has been reported to demonstrate activities relevant to psoriasis therapy (359). *In vitro*, Xu *et al* 1997 reported that an extract showed effects against liver injury in mice (360). In RAW 264.7 cells stimulated by LPS, pretreatment with fraxinellone demonstrated anti-inflammatory activity

by inhibiting nitric oxide (NO) and prostaglandin E2 (PGE_2) and it also dose-dependently reduced the expression of iNOS and COX-2 which was due to the inhibition of NF-$_{\kappa}$B (361). In a mouse hepatitis model, Sun *et al* 2009 reported that fraxinellone demonstrated liver protective effects and it reduced both serum transaminases and liver damage (235). Chang *et al* 2001 reported that of seven compounds isolated from *D. dasycarpus*, dictamnoside A showed the greatest stimulating effect on T-cell proliferation in a mouse splenocyte assay (362).

In a mouse model of pruritus induced by compound 48/80, a *D. dasycarpus* extract inhibited histamine release from peritoneal mast cells and inhibited scratching behaviour induced by compound 48/80, histamine and serotonin in a dose-dependent fashion (363).

Tse *et al* 2006 reported that a root-bark extract was ineffective against the proliferation of human epidermal keratinocytes *in vitro* (356).

7.4.12 Experimental studies on borneol

Borneol is a terpene that can be isolated from numerous plants, notably from *Dryobalanops aromatica,* or synthesised (364). It is frequently used in topical preparations as a transdermal penetration enhancer (365). A number of studies have shown that borneol enhanced absorption. In rats, it increased the penetration of propranolol hydrochloride (366) and promoted the transdermal penetration of a number of components of herbal medicines including curcumin (367). Borneol increased the penetration of ligustrazine in pigs (368) and jasminoidin in frogs (369). Borneol has also been reported to assist in wound healing (370, 371).

7.5 Summary

The above herbs that were used in the RCTs have each been the subject of multiple experimental studies. Although there is considerably variation between these herbs in the number of studies and the scope of the research, all have shown effects which could be relevant to psoriasis therapy. These are summarised below.

7.5.1 Inflammation

Anti-inflammatory activity has been reported for a number of herbs and for their constituent compounds. For *O. diffusa* anti-inflammatory effects have been found for the aqueous extract and for the compounds ursolic acid (UA), oleanolic acid (OA), and hentriacontane and for the related compound oleanolic acid acetate (OAA). An aqueous extract of *Rehmannia glutinosa* has shown actions against inflammation as have a fraction that contained rehmapicrogenin and cinnamic acid, a polysaccharide fraction (LRPS) and the compound catapol. A lipid-soluble extract of *S. miltiorrhiza* showed anti-inflammatory effects.

Indirubin isolated from *Indigo naturalis* has shown an anti-inflammatory effect. A hydroalcoholic extract of *Mahonia aquifolium* was shown to dose-dependently inhibit inflammatory reactions and it main active component berberine, which is also found in other Mahonia species as well as in *Coptis chinensis* (huang lian) has received much attention as an anti-inflammatory compound.

Extracts from *S. flavescens* root have shown biological activity against inflammation, allergy and arthritis. The compounds responsible for its anti-inflammatory effects include the alkaloids matrine and oxymatrine, the flavonoid trifolirhizin and the flavanone kurarinone. An extract of *L. erythrorhizon* and the naphthoquinone pigment shikonin have demonstrated anti-inflammatory actions. Osthole, an active compound in *Cnidium monnieri* has anti-inflammatory effects and fraxinellone from *Dictamnus dasycarpus* has shown anti-inflammatory and liver protective effects.

7.5.2 Proliferation

A number of plants have been demonstrated to reduce proliferation and/or induce the apoptosis of keratinocytes.

An ethanol extract and the active ingredients (ursolic acid, oleanolic acid) of *O. diffusa* can induce apoptosis. For *S. miltiorrhiza* extracts, a polysaccharide (SMP-W1) fraction and the compound tanshinone IIA have all shown anti-proliferative effects.

Both an ethanolic extract of *Aloe vera* and the compound aloe emodin can exert anti-proliferative actions. Indirubin from *Indigo naturalis* has an anti-proliferative effect and *Camptotheca* extracts as well as the compound camptothecin (CPT) have potent biological actions against proliferation. Camptothecin can promote cell differentiation. *Mahonia* extracts have been reported to exert anti-mutagenic/anti-carcinogenic effects.

Extracts from *S. flavescens* have been shown to induce apoptosis, the flavonoid trifolirhizin and the flavanone kurarinone have also demonstrated anti-proliferative effects. For *L erythrorhizon*, an extract and the compound shikonin have shown anti-proliferative actions. An extract of *C. monnieri* and the compound osthole can exert anti-proliferative actions. Dictamnoside A, an active constituent from *D. dasycarpus*, can exert anti-proliferative effects but a root-bark extract from the herb was reported to be ineffective.

7.5.3 Angiogenesis

An anti-angiogenic effect was reported for shikonin.

7.5.4 Wound healing & tissue repair

Aloe vera mucilage has a tissue repair effect. An aqueous extract of *L. erythrorhizon* promoted wound-healing and both shikonin and alkannin enhanced proliferation of granulation tissue. Both oleanolic and ursolic acids enhanced recovery of epidermal barrier function. Borneol can also assist in wound healing.

7.5.5 Pruritus

Aloe vera cream has been demonstrated to be effective for pruritus. Extracts from *Cnidium* and *Sophora* has shown dosage-dependent anti-pruritic effects an extract of *D. dasycarpus* has been shown to be effective against pruritus.

Chapter 8: Large-scale biological target and pathway analysis for the main herbs, compounds and APPs

8.1 Introduction

The SRs in chapters 5 and 6 identified a number of herbs that showed promise of efficacy in the clinical management of psoriasis. In chapter 7, an investigation of the experimental studies that have been conducted on these herbs, their extracts, fractions as well as consituent compounds, has shown that these herbs have biological actions of relevance to psoriasis. This investigation also provided indications of how these herbs might act in psoriasis therapy. However, the experimental data on the herbs is principally derived from models that are not specific to psoriasis. Also the scope of the experimental data on the herbs was confined to models of relevance to skin or to the processes of inflammation, proliferation, angiogenesis and wound healing. Consequently, this cannot provide a complete view of the possible actions of the herbs. Moreover, although certain pharmaceuticals (i.e. the APPs) can be used to treat psoriasis symptoms and there has been much progress in the understanding of psoriasis, the underlying causes of psoriasis and the therapeutic targets of relevance to psoriasis remain incompletely defined (34). Also, the APPs that show efficacy in psoriasis tend not to be drugs that are specific for psoriasis (35, 135). Each of these issues presents challenges when exploring the potential actions of herbs in psoriasis management and the protein upon which they may act.

Although the optimal drug targets for psoriasis therapy remain incompletely defined, some of the newer anti-psoriatic drugs, such as the T-cell targeted drug alefacept and the TNF inhibitor etanercept have well-defined targets and much is known about the proteins involved in the pathological pathways upon which these drugs act (372). In contast, for drugs such as methotrexate while some of its targets have been identified, these relate to other diseases and its actions in psoriasis are not yet fully understood (373).

Pharmacotherapy mostly exerts its effect by binding to a cavity and regulating the activity of its protein target(s). Exploration and investigation of therapeutic targets can facilitate

screening for potential new drugs and drug discovery for a specific disease. Knowledge of the targets of drugs that are known to be effective for a particular disease can assist in identifying and/or designing new drugs for that disease (374).

In the case of herbal medicines, each contains a number of compounds and for some herbal medicines many compounds have been characterized. Consequently it is possible that the herbal medicine is acting upon more than one target. This issue is compounded when herbs are combined in a formula. In recent years there has been interest in developing methods for applying *in silico* methods that aim to analyse the relationships between the compounds contained in a herbal medicine and/or a combination of herbal medicines and protein targets relevant to a particular disease (375-380).

In psoriasis therapy, APPs can target the hyperproliferation of keratinocytes via proteins such as peroxisome proliferation activation receptor (PPAR) and transforming growth factor-beta (TGFbeta). Inflammation can be targeted via inhibition of pro-inflammatory factors including Interferon gamma (INFgamma), Cyclooxygenase (COX), Tumour necrosis factor (TNF) and various interleukins (IL) including those with pro-inflammatory (IL-1, IL-6, IL-8 & IL-12) and with anti-inflammatory (IL-4, IL-10, IL-11, IL-13) effects. Angiogenesis is another process that is important in plaque development with targets such as Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) having received attention. Leukocyte migration is another process that has been targeted in order to reduce inflammation, with proteins such as Intercellular adhesion molecule-1 (ICAM-1) being targeted by biologic APPs such as efalizumab (381, 382).

In order to further explore how the 12 herbs discussed in chapter 7 may act with regard to psoriasis, and to investigate whether the actions of these herbs can provide insight into the targets of psoriasis therapy, the following chapter employs databases to identify the likely targets of the herbs and the pathways that they may affect.

In addition, this component of the research aimed to develop a method for *in silico* investigations that can be used to link the results of systematic reviews of clinical trials of

HMs (chapters 5-6) and the results of experimental studies (chapter 7) to the processes of drug discovery and to provide directions for target-directed drug discovery from HMs. The method employed in this chapter is still under development so the results must be considered to be preliminary.

A number of databases of natural products and their constituent compounds have been developed (383, 384). These include databases that focus on Chinese herbs such as Chemical Database of Traditional Chinese Medicine (CHEM-TCM) [http://chemtcm.com/] (385), and Herbal Ingredients' Targets (HIT) [http://lifecenter.sgst.cn/hit/] (386). Of these, HIT contains extensive data on compounds and their targets and is available for free public access.

With the expansion of therapeutic target databases and the development of methods for computational prediction of biological activity, *in silico* tools for target-directed exploration have become widely available (377). These online databases can greatly assist in drug-target directed drug discovery and can be integrated with other approaches.

This investigation involved the following main stages.

1. Firstly, the known compounds contained in the plant species used for each of the 12 MHs were identified.
2. Then database searches were used to identify the biological targets of each of the herbs. Also, the targets of the pharmaceuticals used for psoriasis therapy (i.e APPS) were identified and these were compared with the known targets of each of the herbs and their constituent compounds. This allowed the identification of herbs that shared targets with these APPs. These herbs were defined as 'APP-like'.
3. Since, the known targets of APPs may not be the only targets of relevance to psoriasis therapy, a further investigation was conducted of the likely pathways through which the herbal compounds may act based on all their known protein targets. This was undertaken for four of the 12 herbs.

Research questions:

1. Do any of the promising herbs have targets similar to those of the APPs?
2. What are the likely therapeutic targets of the most promising herbs?
3. Which biological pathways could these herbs act upon?

8.2 Method

8.2.1 General approach

Three main databases were employed in the *in silico* investigation. The targets of the herbs and the drug (APP) targets were identified using DrugBank and HIT. Following this investigation, the identified targets were entered into to the predictive PANTHER database to undertake a large scale investigation of the biological pathways upon which the herbs are likely to act. Figure 8.1 shows a schema of the process (Fig. 8.1).

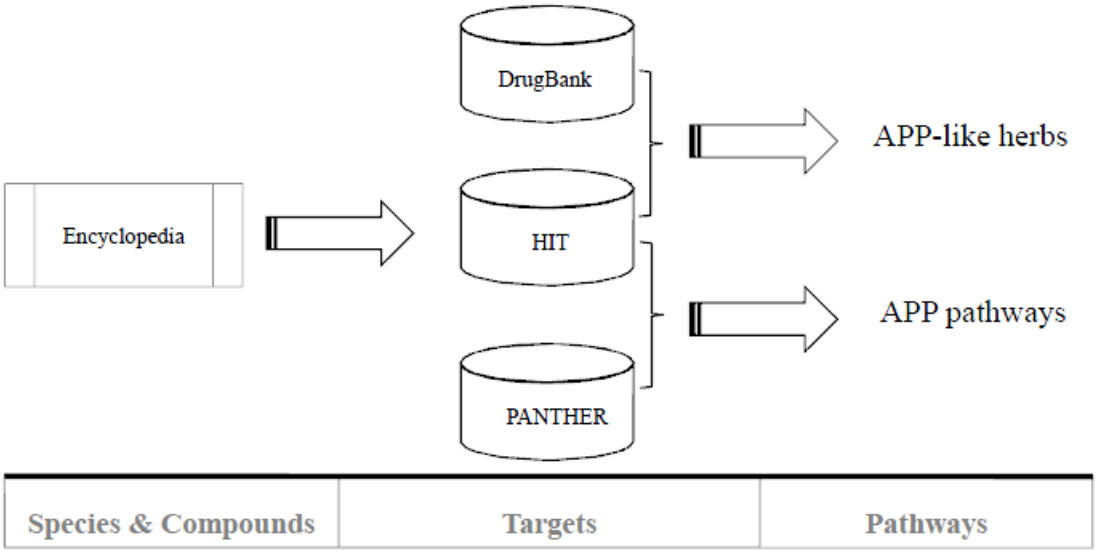

Fig. 8.1 Diagram of components of the large-scale biological targets *in silico* analysis

8.2.2 Databases and resources

The *in silico* investigations in this section intended not only to investigate the likely targets of the 12 herbs but also aimed to develop a more broadly applicable model for future investigations of herbs and their therapeutic targets in other diseases. Therefore, the

resources selected are all available for public access and all are available in English. In the case of the on-line databases, they all provide free access. The main resources are as follows:

- Encyclopaedia of traditional Chinese medicines: molecular structures, pharmacological activities, natural sources and applications (Encyclopaedia of TCM) (387); and the databases:
- HIT (China) (386);
- DrugBank (Canada) (388); and
- PANTHER (USA) (389).

The application and features of each resource is detailed below.

8.2.2.1 Encyclopaedia of TCM

Encyclopaedia of TCM is a six volume work that provides a comprehensive survey of Chinese herbs including the source species and chemical ingredients. It is extensively indexed can be searched in a systematic manner (387). For each of the herbs, the species that can be used were identified using *Encyclopaedia of TCM*. In order to capture the all the possible plants that may have been used in clinical studies, both the main species and secondary species were included. The chemical constituents of each species were identified using *Encyclopaedia of TCM* and the journal articles cited in chapter 7.

8.2.2.2 Herbal Ingredients' Targets database (HIT)

Herbal Ingredients' Targets (HIT, http://lifecenter.sgst.cn/hit/) is a curated on-line databse that is available in English and Chinese. It contains herb names written in Chinese pin yin and Latin names, compound names and chemical structures. It is searchable online via standard queries and keywords as well as by chemical structure similarity search (386). The interface is well designed and is particularly suited to searches of targets that correspond to a specific herb or constituent (Fig. 8.2). The database contains 5,208 entries which include 1,301 known protein targets which are linked to 586 herbal active constituents from more than 1,300 herbs. HIT is linked to other target databases including DrugBank, KEGG (Kyoto Encyclopedia of Genes and Genomes) and Uniprot (Protein knowledgebase).

The HIT database was used to identify the therapeutic targets of each of the compounds in each of the herbs. The searches of HIT provided lists of direct and indirect targets, which may or may not be relevant to psoriasis.

Fig. 8.2 Interface of Herbal Ingredients' Targets Database (HIT)

8.2.2.3 DrugBank database

DrugBank (http://www.drugbank.ca) is a curated bioinformatics and cheminformatics database that combines chemical, pharmacological and pharmaceutical drug data with comprehensive drug target information including sequence, structure and pathway (388, 390). It contains about 4,900 drug entries including FDA approved and experimental drugs as well

as nutraceuticals. The version used in the searches, DrugBank 3.0, included 1,768 approved-drug targets, 1,424 FDA-approved drugs as well as 68 withdrawn drugs. DrugBank has been widely cited (> 400 citations), is integrated into many popular databases (>20), and is highly used by healthcare professionals and the general public with more than 4 million internet-hits (388). DrugBank accepts the advanced Google-style searching and boolean logic (AND, OR, NOT operations) on its interface (Fig. 8.3).

The DrugBank database was used to identify the targets of the APPs used for psoriasis, and drugs in development for psoriasis. This provided a list of drug targets of likely relevance to psoriasis.

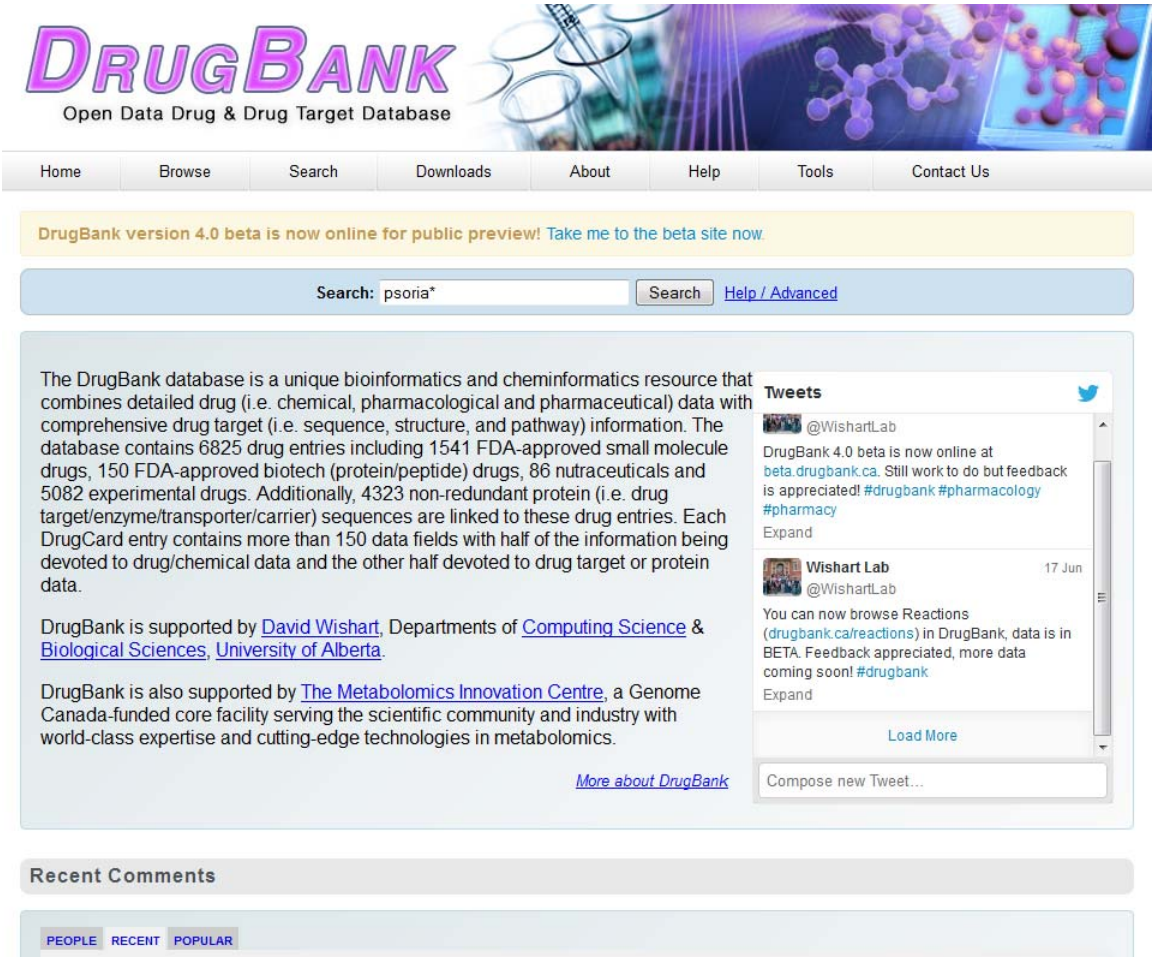

Fig. 8.3 Interface of DrugBank

8.2.2.4 PANTHER database

The PANTHER (Protein ANnotation THrough Evolutionary Relationship) Classification System (http://www.pantherdb.org/) classifies proteins and their genes for a variety of species based on their evolutionary relationships. It is designed to facilitate high-throughput analysis and can be used in genetic and drug-discovery research. It has more than 7,000 registered users, 600-800 daily users and 14,000 monthly users with 3,600 citations. Registered users can store data in their account for further usage.

Version 8.0 was used in the searches. It contains 640,000 proteins from 7,729 families among 82 genomes with 176 expert-curated pathways. (389). Based on the protein sequence corresponding to a biological target, PANTHER 8.0 can predict the relevant molecular function(s), biological process(es), cellular component(s), protein class and biological pathway(s).

PANTHER was used to predict the likely biological processes and pathways, through which the APP-like herbs might act based on the targets identified using HIT (Fig. 8.4).

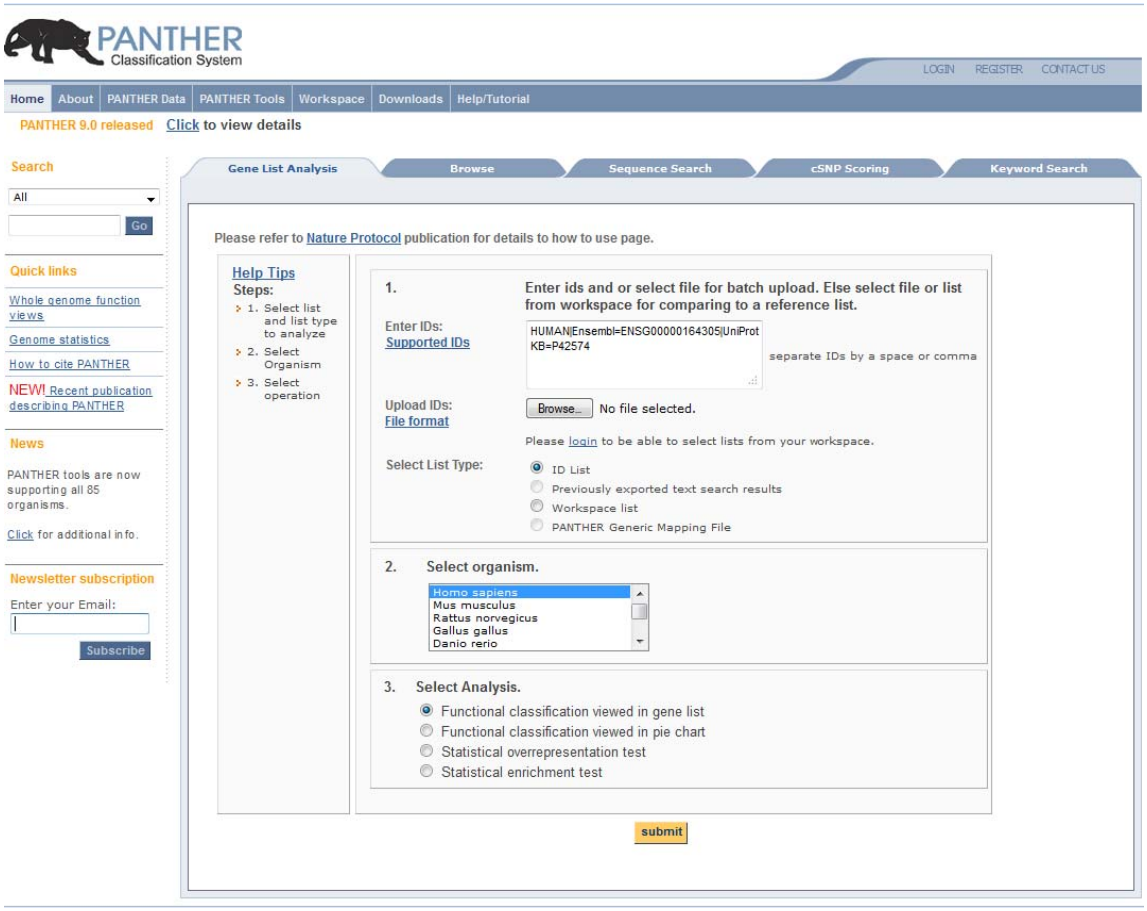

Fig.8.4 Interface of PANTHER (Protein ANnotation THrough Evolutionary Relationship)

Additional resources included: 'Protein knowledgebase' (Uniprot) [http://www.uniprot.org], which provides protein names and functions; the GenomeNet Database (KEGG) [http://www.genome.jp] which provides pathway information; and Gene Cards [http://www.genecards.org/] which provides comprehensive gene-related data, including clinical, and functional information. Uniprot and GeneCards were mainly used for target information while KEGG was mainly used for pathway information. However, these databases have many uses and show overlap with, HIT, DrugBank and PANTHER.

It should be noted that the nomenclature of targets (full names and acronyms) and of pathways can vary from database to database and from publication to publication. Also the names used in HIT can differ from those used in PANTHER. In the results below, full names are used for targets in the first instance with the acronym being used in subsequent mentions.

8.2.3 Procedures for *in silico* analysis

The *in silico* investigation involved a series of stages and processes as follows:

Target level analysis

1. Encyclopaedia of TCM: The indices (in volume 6) were used to search the Chinese names for each of the 12 herbs (in Chinese characters) to identify the Latin names of each of the species that could be used as these herbs. The initial species list was filtered to remove infrequently used species since these were unlikely to correspond to the herbs used in the clinical trials. For each of the species, the plant code was recorded and the plant codes were used to search for the chemical constituents for each species.
2. HIT: This database was used to identify the known therapeutic targets for each compound in each herb. The compounds identified from the search of Encyclopaedia of TCM were each entered into the compound search field in HIT and the resultant list of Target names, Target IDs and Target types were recorded for each herb in an Excel spreadsheet.
3. DrugBank: This database was used for identifying drugs used for psoriasis and the targets of these drugs. To identify drugs used for psoriasis the term: psoria* was entered into the search field. The name of each drug identified in DrugBank was recorded in Excel. This provided the list of APPs.
4. APP targets: For each APP, their targets derived from DrugBank (including enzymes, carriers and transporters) were listed in Excel together with information on their actions and which category they belonged to. For example, for the APP tazarotene one of its targets is retinoic acid receptor alpha and its action is as an agonist. Enzymes, carriers and transporters for which no action was listed were discarded from the list. This provided the data set for the known APP targets. Such targets could be expected to be druggable but they may not all be relevant to psoriasis (374).
5. Target screening: It is likely that a number of the targets of the herbs and compounds identified via the HIT searches were not of relevance to psoriasis therapy. In contrast,

the targets identified by the searches of DrugBank are more likely to be relevant to psoriasis therapy, although they are not necessarily the only relevant targets. In order to identify which herbs are likely to have activity in psoriasis, the list of herb/herbal compound targets was filtered using the list of APP targets, excluding the targets for which the action is listed as 'unknown' in DrugBank. This provided a short list of targets and consequently a set of herbs that shared targets with the known targets of the APPs. These were defined as 'APP-like herbs'. For each species the specific APPs with which there were shared targets were identified. It was expected that this data could provide insight into the therapeutic applications of the herbs and could provide directions for further research.

6. Selection of the most promising APP-like herbs for further investigation: Based on the combined results of the HIT and DrugBank searches and subsequent filtering of targets, the herbs were ranked according to the number of targets they shared with the APPs. This enabled selection of a short-list of herbs for the pathway level analysis.

Pathway level analysis

1 PANTHER: This database was used to further explore the likely actions of the most promising APP-like herbs. For each of these herbs, each of their known protein targets was entered into the Keyword search. Since PANTHER contains data for many species, all searches were conducted using the 'homo sapiens' setting. For each target, the identified Gene ID was saved as txt in a Notepad file. One Notepad file was created for each species. This file contained all the Gene IDs for all the known therapeutic targets of all the compounds that are known to be active in the species. It should be noted that some compounds that have been identified as present in a species have no known activity and consequently no known targets.

2 The texts from each Notepad file were sequentially uploaded into the Gene List Analysis field in PANTHER. These files usually contained multiple Gene IDs. The results for each file identified five aspects for the particular species: molecular function(s), biological process(es), cellular component(s), protein class and

pathway(s). The data for each was saved as text in Excel. The Excel files were sorted to identify which were the most commonly identified pathways for each species.

3 For each of the most commonly identified pathways, all the proteins that PANTHER identified as a component of the pathway, excluding upstream and downstream proteins, were entered into Excel. Since the nomenclature used by PANTHER and by HIT differ, cross-referencing was undertaken regarding the short and long names used for the proteins in both databases (see Appendix 19).

4 Since it was impractical to cross reference every target in every herb to every pathway, herbs were shortlisted for the HIT / PANTHER comparison. Also, comparion was undertaken for a limited number of pathways. See below for the shortlising processes.

5 For each of the pathways, the proteins identified in PANTHER were cross-referenced to the targets identified in HIT for each of the shortlisted herbs.

6 The proteins that were identified as targets of the compounds contained in the herbs were identified for each pathway.

8.3 Results

8.3.1 Constituents of the promising herbs

The 4 SRs identified 12 herbs as promising for psoriasis management. The names of these herbs and their main source species are as follows: Bai hua she she cao (*Oldenlandia diffusa),* Di huang *(Rehmannia glutinosa),* Dan shen *(Salvia miltiorrhiza),* Lu hui *(Aloe vera* and *Aloe ferox),* Qing dai *(Indigo naturalis* from *Isatis* or *Baphicacanthus* species*),* Xi shu *(Camptotheca acuminata),* Gong lao mu *(Mahonia aquifolium* and other *Mahonia* species), Ku shen *(Sophora flavescens), Zi cao (Lithospermum erythrorhizon* and *Arnebia* species*),* She chuang zi *(Cnidium monnieri),* Bai xian pi *(Dictamnus dasycarpus)* and Bing pian (borneol from *Dryobalanops aromatica* or synthetic sources).

The Encyclopedia of TCM identified 44 specific species, forms and/or varieties relating to these 12 herbs and one additional species, Tai wan ma lan (*Strobilanthes formosanus*), was

identified from a clinical trial (214). Table 8.1 lists the plant code from the *Encyclopedia of TCM*, the Chinese name and the Latin names of 45 species, forms and varieties.

The herbs Bai hua she she cao, Di huang, Xi shu, She chuang zi, Bai xian pi and Ku shen were each derived from a single species although Di huang was listed under four plant codes due to the different forms of preparation of the same species (*Rehmannia glutinosa)* as follows: the steamed root (shu di huang), dry unprocessed form of the root (gan di huang) and the fresh root (sheng di). Bing pian can be a synthetic product but its main natural source is from *Dryobalanops aromatica.* For the other herbs, they can derive from multiple species so each of the species in clinical use in Chinese medicine was included (Table 8.1).

Table 8.1 List of herbs, plant codes and species from Encyclopedia of TCM

Herb name (pin yin)	**Plant Code**	**Chinese names**	**Chinese names (pin yin)**	**Species (Latin names)**
bai hua she she cao	T4485	白花蛇舌草	bai hua she she cao	*Oldenlandia diffusa [Syn. Hedyotis diffusa]*
di huang	T5445	干地黄	gan di huang	*Rehmannia glutinosa [Syn. R. glutinosa f. huechingensis]*
di huang	T5446	熟地黄	shu di huang	*Rehmannia glutinosa [Syn. R. glutinosa f. huechingensis]*
di huang	T5447	鲜地黄(生地)	xian di huang (sheng di)	*Rehmannia glutinosa [Syn. R. glutinosa f. huechingensis]*
di huang	T5448	紫地黄	zi di huang	*Rehmannia glutinosa var. purpurea*
dan shen	T5681	白花丹参	bai hua dan shen	*Salvia miltiorrhiza f. alba*
dan shen	T5680	丹参	dan shen	*Salvia miltiorrhiza*
dan shen	T5692	拟丹参	ni dan shen	*Salvia sinica*
dan shen	T5689	紫丹参	zi dan shen	*Salvia przewalskii var. mandarinorum*
lu hui	T0348	斑纹芦荟	ban weng lu hui	*Aloe vera var. chinensis*
lu hui	T0346	多种芦荟提取物	duo zhong lu hui ti qu wu	*Aloe spp.*
lu hui	T0338	好望角芦荟	hao wang jiao lu hui	*Aloe ferox*
lu hui	T0347	芦荟(库拉索芦荟)	lu hui (ku lao suo lu hui)	*Aloe vera [Syn. A. barbadensis]*
qing dai	T3475	板蓝根	ban lan geng	*Isatis indigotica*
qing dai	T3476	大青叶	da qing ye	*Isatis indigotica*

qing dai	T3477	欧洲菘蓝	ou zhou song lan	*Isatis tinctoria [Syn. I. indigotica]*
qing dai	T0866	马蓝根	ma lan geng	*Baphicacanthus cusia [Syn.Strobilanthes cusia]*
qing dai	T0867	马蓝叶	ma lan ye	*Baphicacanthus cusia [Syn.Strobilanthes cusia]*
qing dai	NA	台湾马蓝	tai wan ma lan	*Strobilanthes formosanus**
xi shu	T1162	喜树	xi shu	*Camptotheca acuminata*
gong lao mu	T4072	城口十大功劳	cheng kou shi da gong lao	*Mahonia shenii*
gong lao mu	T4076	川滇十大功劳	chuan dian shi da gong lao	*Mahonia veitchiorum*
gong lao mu	T4066	华南功劳木	hua nan gong lao mu	*Mahonia japonica*
gong lao mu	T4067	华南功劳叶	hua nan gong lao ye	*Mahonia japonica*
gong lao mu	T4068	华南功劳子	hua nan gong lao zi	*Mahonia japonica*
gong lao mu	T4056	十大功劳叶	shi da gong lao ye	*Mahonia bealei*
gong lao mu	T4063	细叶功劳叶	xi ye gong lao ye	*Mahonia fortunei*
gong lao mu	T4054	尖叶十大功劳	jian ye shi da gong lao	*Mahonia aqulifolium*
gong lao mu	T4061	宽苞十大功劳	kuan bao shi da gong lao	*Mahonia eurybracteata*
gong lao mu	T4055	十大功劳木	shi da gong lao mu	*Mahonia bealei*
gong lao mu	T4057	十大功劳子	shi da gong lao zi	*Mahonia bealei*
gong lao mu	T4064	细柄十大功劳	xi bing shi da gong lao	*Mahonia gracilipes*
gong lao mu	T4062	细叶功劳木	xi ye gong lao mu	*Mahonia fortunei*

gong lao mu	T4063	细叶功劳叶	xi ye gong lao ye	*Mahonia fortunei*
gong lao mu	T4058	小果十大功劳	xiao guo shi da gong lao	*Mahonia bodinieri*
ku shen	T6031	苦参	ku shen	*Sophora flavescens [Syn. S. angustfolia]*
ku shen	T6032	苦参实	ku shen shi	*Sophora flavescens [Syn. S. angustfolia]*
zi cao	T4500	滇紫草	dian zi cao	*Onosma paniculatum*
zi cao	T0649	假紫草	jia zi cao	*Arnebia guttata*
zi cao	T4499	细花滇紫草	xi hua dian zi cao	*Onosma hookeri*
zi cao	T0648	新藏假紫草	xin zang jia zi cao	*Arnebia euchroma*
zi cao	T3881	紫草	zi cao	*Lithospermum erythrorhizon*
she chuang zi	T1582	蛇床子	she chuang zi	*Cnidium monnieri*
bai xian pi	T2167	白鲜皮	bai xian pi	*Dictamnus dasycarpus*
bing pian	T2274	冰片	bing pian	*Dryobalanops aromatica*

*Retrieved from Lin *et al* 2008.

8.3.2 Biological targets for the compounds in each herbs identified using HIT

In total, 482 different constituent compounds were identified via *Encyclopedia of TCM* for the 45 species, forms and varieties. When these compounds were entered into the HIT database, a total of 350 biological targets were identified. The database searches identified numerous targets for the compounds included in each of the 12 herbs. These targets are presented separately for each herb in the tables in Appendix 1-12.

The names of the proteins which form the targets can vary considerably according to the source and multiple acronyms are used in the literature, so a table of acronyms and the full target names in HIT and PANTHER is provided in Appendix 19.

It should be noted that some of the compounds identified via *Encyclopedia of TCM* did not retrieve any information from HIT. Also, some compounds can have multiple names which have been noted in the results.

8.3.2.1 Compounds and targets for Bai hua she she cao (*Oldenlandia diffusa*)

Of the 14 compounds contained in *Oldenlandia diffusa,* three compounds returned results from HIT: ursolic acid, oleanolic acid and stigmasterol. Notable among the targets of these compounds are caspase-3 and 9, which are targets of all three compounds; apoptosis regulator BAX [Bax] (ursolic acid, stigmasterol), apoptosis regulator Bcl-2 (ursolic acid, stigmasterol), intercellular adhesion molecule 1 [ICAM1] (oleanolic acid, ursolic acid), transcription factor AP-1 (ursolic acid, stigmasterol), tumour necrosis factor [TNF] (ursolic acid), prostaglandin G/H synthase 1 & 2 [COX-1 & 2] (ursolic acid), Transcription factor p65 [NF kappa B] (ursolic acid), NF-kappa-B inhibitor alpha [NFKBIA] (ursolic acid), Nitric oxide synthase, inducible [iNOS] (ursolic acid), Cyclin-dependent kinase inhibitor 1 [p21] (ursolic acid), Cellular tumor antigen p53 [p53] (ursolic acid) and Prostaglandin E2 receptor EP3 subtype [PGE2-R] (ursolic acid) (see full list in Appendix 1).

8.3.2.2 Compounds and targets for Di huang (*Rehmannia glutinosa*)

In total, 94 compounds were identified for Di huang, all of which were for the primary species *Rehmannia glutinosa.* Of these, the compounds that retrieved the largest numbers of targets were cinnamic acid (*aka* rosmarinic acid, caffeic acid), aucubin, catalpol, geniposide, hexadecanoic acid, caprylic acid, lauric acid and stigmasterol.

The most frequently retrieved targets were: apoptosis regulator Bcl-2 (aucubin, catalpol, geniposide, hexadecanoic acid, stigmasterol), caspase-3 (catalpol, cinnamic acid, stigmasterol, succinic acid), interleukin-6 [IL-6](aucubin, hexadecanoic acid, lauric acid, γ-aminobutyric acid), transcription factor p65 [NF kappa B](aucubin, cinnamic acid, hexadecanoic acid, lauric acid), apoptosis regulator BAX (aucubin, cinnamic acid, stigmasterol), tumour necrosis factor [TNF] (aucubin, cinnamic acid, hexadecanoic acid), prostaglandin G/H synthase 2 [COX-2] (cinnamic acid, hexadecanoic acid, lauric acid), prostaglandin G/H synthase 1 [COX-1] (cinnamic acid), nitric oxide synthase, inducible [iNOS](catalpol), cytochrome P450 1A1 (cinnamic acid), aldo-keto reductase family 1 member C1 [AKR1C1](cinnamic acid), and C-C motif chemokine 2 [MCP-1] (Appendix 2).

8.3.2.3 Compounds and targets for Dan shen (*Salvia miltiorrhiza*)

For the three closely related Dan shen species *Salvia miltiorrhiza*, *S. sinica* and *S. przewalskii*, a total of 76 compounds were identified. The main compounds included tanshinones I & IIa, cryptotanshinone, dihydrotanshinone I, salvianolic acids A & B, ursolic acid, lithospermic acid B (*aka* salvianolic acid B), danshensu (*aka* salvianic acid A), caffeic acid (*aka* rosmarinic acid, cinnamic acid), and tigogenin.

The main targets identified from HIT included: Apoptosis regulator Bcl-2 (salvianolic acid A, tanshinone IIa, ursolic acid), Bcl-2-like protein 1 [BCL2L1, BCLX] (cryptotanshinone, dihydrotanshinone I, ursolic acid), Apoptosis regulator BAX (ursolic acid), caspase-3 (dihydrotanshinone I, lithospermic acid B, salvianolic acids A & B, tanshinone IIa, ursolic acid), G1/S-specific cyclin-D1 [CCND1, BCL-1] (cryptotanshinone, dihydrotanshinone I, salvianolic acid A, ursolic acid), transcription factor p65 [NF kappa B] (cryptotanshinone, danshensu, lithospermic acid B, tanshinone IIa, ursolic acid), endothelin-1 [RT-1, EDN-1] (cryptotanshinone, tanshinone IIa), intercellular adhesion molecule 1 [ICAM1] (lithospermic acid B, salvianolic acid B, tanshinone I, ursolic acid), vascular endothelial growth factor A [VEGF-A] (lithospermic acid B, salvianolic acid B, tanshinone I, ursolic acid), Cyclin-dependent kinase inhibitor 1 [CAP20, CDKN1] (salvianolic acid A, tanshinone IIa, ursolic acid), probable E3 ubiquitin-protein ligase HERC5 (dihydrotanshinone I, salvianolic acid A, ursolic acid), vascular cell adhesion protein 1 [VCAM-1] (lithospermic acid B, salvianolic acid B, tanshinone I), cytochrome P450 1A1, 1A2 & 3A4 (tanshinone IIa, caffeic acid), prostaglandin G/H synthase 1 & 2 [COX 1&2] (caffeic acid, ursolic acid, lithospermic acid B, salvianolic acid B, tigogenin), tumour necrosis factor [TNF] (caffeic acid,

cryptotanshinone, ursolic acid), Activator of 90 kDa heat shock protein ATPase homolog 1 [p38, AHSA1] (tanshinone IIa), Mitogen-activated protein kinase 1 [ERK2, MAPK1] (tanshinone IIa), Poly [ADP-ribose] polymerase 4 [PARP] (tanshinone IIa), Actin, aortic smooth muscle [ACTA2, α-SMA] (salvianolic acid B *aka* lithospermic acid B) (Appendix 3).

8.3.2.4 Compounds and targets for Lu hui (*Aloe vera*)

Searches located 49 compounds in *Aloe vera* and *Aloe ferox*. Major compounds included hexadecanoic acid, lauric acid, linolenic acid (*aka* alpha-linolenic acid), p-coumaric acid, rutin, sucrose, aloin and aloe emodin.

Therapeutic targets were only identified for *Aloe vera* and the variety *chinensis*. The most common targets were: interleukin-6 [IL-6] (hexadecanoic acid, lauric acid, rutin), transcription factor p65 [NF kappa B] (hexadecanoic acid, lauric acid, linolenic acid, rutin), prostaglandin G/H synthase 2 [COX 2] (hexadecanoic acid, lauric acid, linolenic acid), tumor necrosis factor [TNF] (hexadecanoic acid, rutin), Caspase-3 (succinic acid, rutin), Apoptosis regulator Bcl-2 (hexadecanoic acid), and Collagen alpha-1(I) chain [COL1A1](hexadecanoic acid) (Appendix 4).

8.3.2.5 Compounds and targets for Qing dai (*Indigo naturalis*)

In total 43 compounds were identified for three species: *Isatis indigotica* (*aka I. tinctoria*), *Baphicacanthus cusia*, and *Strobilanthes formosanus*. The main compounds were: indirubin, lupeol, salicylic acid, sucrose, tryptanthrine, β-sitosterol, indigotin, hexadecanoic acid. Indirubin was found in all three species.

The most frequently identifed targets were Caspase-3 & 9 (lupeol, tryptanthrine, β-sitosterol), Apoptosis regulator Bcl-2 (lupeol, β-sitosterol, hexadecanoic acid), cyclin-dependent kinase inhibitor 3 [CDKN3] (indirubin), cytochrome P450 1A1 & 1A2 (indirubin, sucrose), glycogen synthase kinase-3 beta [GSK-3 beta] (indirubin), interferon gamma [IFN gamma] (indirubin), multidrug resistance protein 1 [ABCB1] (tryptanthrine), serum paraoxonase/arylesterase 1 [PON1] (salicylic acid, β-sitosterol), tumour necrosis factor [TNF] (hexadecanoic acid), Transcription factor AP-1 [Ap-1] (β-sitosterol), transcription factor p65 [NF kappa B] (Salicylic acid), Interleukin-4 [IL 4] (salicylic acid), Interleukin-10 [IL 10] (hexadecanoic acid), and Protein kinase C alpha type [PRKCA] (β-sitosterol) (Appendix 5).

8.3.2.6 Compounds and targets for Xi shu (*Camptotheca acuminata*)

There were 28 compounds derived from *Camptotheca acuminata* that were identified from *Encyclopedia of TCM*. These compounds included quercetin, hyperin, and camptothecin.

The main targets were: apoptosis regulator bax (hyperin, quercetin), caspase-3 (hyperin, quercetin), Apoptosis regulator Bcl-2 (quercetin), Transcription factor AP-1 [AP1](quercetin), Transcription factor p65 [NF kappa B] (quercetin), catalase [CAT] (hyperin, quercetin), superoxide dismutase [Cu-Zn] (hyperin, quercetin), ATP-binding cassette sub-family G member 2 [ABCG2] (quercetin, camptothecin), cytochrome P450 1A1, 1A2 & 3A4 (quercetin), myeloperoxidase [MPO] (quercetin), prostaglandin G/H synthase 1 & 2 [COX 1 & 2](quercetin), tumour necrosis factor [TNF] (quercetin), Inhibitor of nuclear factor kappa-B kinase subunit alpha [IKK alpha] (quercetin), Interferon gamma [IFN gamma] (quercetin), Interleukins 1A/B, 2, 6, 8, 10 (quercetin), C-C motif chemokine 2 [CCL2] (quercetin), DNA topoisomerase 1 [TOP1] (quercetin, camptothecin), DNA topoisomerase 2-alpha [TOP2A] (quercetin), and Vascular endothelial growth factor A [VEGF-A] (quercetin) (Appendix 6).

8.3.2.7 Compounds and targets for Gong lao mu (*Mahonia aquifolium*)

Ten compounds were identified from the following nine species: *Mahonia aqulifolium, M. shenii, M. veitchiorum, M. japonica, M. fortunei, M. eurybracteata, M. bealei, M. gracilipes, M. bodinieri*. Berberine was the predominant compound which occurred in multiple species. The other main compounds included: jatrorrhizine, palmatine, coptisine, magnoflorine and isotetrandrine.

The most common targets were: G1/S-specific cyclin-D1 [CCND1] (berberine, coptisine), amine oxidase [flavin-containing] A & B [MAO-A & B] (jatrorrhizine, coptisine), Apoptosis regulator BAX (berberine), Apoptosis regulator Bcl-2 (berberine), caspase-3, 8 & 9 (berberine), BH3-interacting domain death agonist [BID] (berberine), Transcription factor AP-1 (berberine), interleukin-4, 6 & 8 (berberine), ATP-binding cassette sub-family G member 2 [ABCG2] (berberine), cytochrome P450 1A1 (berberine), myeloperoxidase [MPO](berberine), prostaglandin G/H synthase 2 [COX-2](berberine), tumour necrosis factor [TNF] (berberine), Vascular endothelial growth factor A [VEGF-A] (berberine), Transcription factor p65 [NF kappa B] (berberine), NF-kappa-B inhibitor alpha [NFKBIA]

(berberine), Nitric oxide synthase, inducible [iNOS] (berberine), Platelet-derived growth factor subunit A [PDGFA] (berberine), Mitogen-activated protein kinase 1 [MAPK1] (berberine), and Interferon gamma [IFN gamma] (berberine) (Appendix 7).

8.3.2.8 Compounds and targets for Ku shen (*Sophora flavescens*)

81 compounds derived from *Sophora flavescens* were identified including matrine, formononetin, cytosine, sophocarpine, sophoramine, sophoridine and kuraridin.

The main targets indentified were as follows: interleukin-6 [IL 6] (matrine, sophocarpine, sophoramine, sophoridine), tumour necrosis factor [TNF] (matrine, sophocarpine, sophoramine, sophoridine), prostaglandin G/H synthase 2 [COX-2] (kuraridin), caspase-3 (matrine), transcription factor p65 [NF-kappa B], Intercellular adhesion molecule 1 [ICAM 1], Transcription factor AP-1 (formononetin), Proto-oncogene c-Fos [FOS] (cytisine) Peroxisome proliferator-activated receptor gamma [PPARG] (formononetin) (Appendix 8).

8.3.2.9 Compounds and targets for Zi cao (*Lithospermum erythrorhizon*)

Overall, 51 constituents were located for 5 species: *Lithospermum erythrorhizon*, *Onosma paniculatum*, *Arnebia guttata*, *Onosma hookeri*, and *Arnebia euchroma*. Shikonin was the major constituent and it was present in four of these species while *Onosma hookeri* contained acetylshikonin. Other important constituents included: caffeic acid, acetylalkannin, isobutyrylshikonin, and β, β-Dimethylacrylalkannin.

The main targets were: Caspase-3 [CASP3] (shikonin), Apoptosis regulator Bcl-2 [BCL2] (shikonin), Bcl2 antagonist of cell death [BBC6] (shikonin), RAC-alpha serine/threonine-protein kinase [AKT1] (shikonin, isobutyrylshikonin), amine oxidase [flavin-containing] A & B [MAO-A] (shikonin), C-C motif chemokine 3 & 5 [CCL3&5] (shikonin), interleukin-1 beta [IL1B] (isobutyryl shikonin), interleukin-4, 6, 8 & 10 [IL4,6,8,10] (shikonin), G1/S-specific cyclin-D1 [CCND1] (shikonin), G1/S-specific cyclin-E1 [CCNE1] (shikonin), Proliferating cell nuclear antigen [PCNA] (shikonin), Serine/threonine-protein kinase PAK 2 [PAK2] (shikonin), Nuclear receptor subfamily 4 group A member 1 [NR4A1] (shikonin), prostaglandin G/H synthase 1 & 2 [COX 1 & 2] (caffeic acid, isobutyrylshikonin), tumour necrosis factor [TNF] (caffeic acid, isobutyrylshikonin), cellular tumor antigen p53 [TP53] (shikonin), vascular endothelial

growth factor receptor 2 [VEGFR2] (shikonin), Angiopoietin-1 receptor [TEK] (shikonin), transcription factor p65 [NF-kappa B] (isobutyrylshikonin), NF-kappa-B inhibitor alpha [NFKBIA] (isobutyrylshikonin), and cytochrome P450 1A1 [CYPIA1] (caffeic acid) (Appendix 9).

8.3.2.10 Compounds and targets for She chuang zi (*Cnidium monnieri*)

21 compounds were identified for *Cnidium monnieri*. Isopimpinellin and osthole were the main compounds. Cytochrome P450 1A1 & 3A4 (isopimpinellin, bergapten), Nitric oxide synthase, inducible (osthole), Nuclear receptor subfamily 1 group I member 2 (isopimpinellin) were the main targets (Appendix 10).

8.3.2.11 Compounds and targets for Bai xian pi (*Dictamnus dasycarpus*)

24 compounds were identified for *Dictamnus dasycarpus*. The major compounds included the dictamnosides (A, B, G, H, I, J, L, M), obaculactone (*aka* limonin) and fraxinellone. The only target identified in HIT was cytochrome P450 3A4 (obaculactone) (Table 8.12). No targets were identified for fraxinellone although targets have been reported (Appendix 11).

8.3.2.12 Compounds and targets for Bing pian (*Dryobalanops aromatica*)

Synthetic borneol mainly contains d-borneol and camphor. For borneol from its natural source, *Dryobalanops aromatica*, 15 ingredients were identified. Oleanolic acid was the main compound for which the following targets were relevant: Caspase-3 & 9 (oleanolic acid) and Heme oxygenase 1 (oleanolic acid). No targets were identified in HIT for d-borneol (Appendix 12).

8.3.3 Identification of APP drug targets using DrugBank

The search of DrugBank located 20 drugs that had been FDA-approved for the management of psoriasis and/or psoriatic arthritis. This included two drugs that have been withdrawn (aminopterin, etretinate). The 20 APP drugs included tazarotene, calcipotriol, acitretin, golimumab, desoximetasone, clobetasol, etanercept, efalizumab, calcitriol, fluticasone propionate, prednisolone, methotrexate, alitretinoin, dimethyl fumarate, alefacept, cyclosporine, aminopterin, etretinate, salicylic acid and methoxsalen.

For these 20 drugs, DrugBank identified 88 targets, enzymes, carriers or transporters on which these drugs are known to have effects. Of these, 17 targets were listed as having 'unknown' actions or their actions were 'not stated', so these were not included in the comparisons with the herbs. In two cases there were carriers/transporters whose actions were 'not stated' with regard to some APPs, whereas actions were listed for other APPs. These were not included when the actions were 'not stated'. The major targets of the APPs included: Glucocorticoid receptor (NR3C1), Prostaglandin G/H synthase 1 & 2 (COX 1 & 2), Retinoic acid receptor (RAR) alpha, beta & gamma-1, RXR-alpha & RXR-beta, T-cell surface antigen CD2 (CD2), Tumour necrosis factor (TNF) and Vitamin D3 receptor (VDR).

69 targets, enzymes, carriers and transporters were cross referenced to the lists of targets identified using HIT. It should be noted that the term 'target' in HIT is broader in meaning than in DrugBank, so the comparison was not limited to the proteins listed in DrugBank as 'targets' but included the enzymes, carriers and transporters as well (Appendix 13).

8.3.3.1. Targets that the herbs shared with the APPs

Following the comparison, 10 targets were found to be common to the APP drug target lists and the lists of targets for the 12 herbs. Of these 12 herbs, 11 had targets in common with at least one of the APPs. The excluded herb was Bing pian (borneol).

Based on the searches of DrugBank and HIT, 12 of the 20 APPs shared at least one target with at least one of the compounds identified in the herbs. The shared targets are as follows:

1) Tumour necrosis factor (TNF) is a target of the biological golimumab and etanercept which are inhibitors of TNF. The following compounds were also identified as having down regulating effects on TNF: ursolic acid, aucubin, cinnamic acid (*aka* caffeic acid), cryptotanshinone, rutin, quercetin, berberine, matrine, sophocarpine, sophoramine, sophoridine and isobutyrylshikonin.

In contrast, hexadecanoic acid was identified by HIT as increasing the expression level or activity of TNF.

The following 9 herbs contained compounds that were identified as down regulating TNF: Bai hua she she cao, Di huang, Dan shen, Lu hui, Qing dai, Xi shu, Gong lao mu, Ku shen and Zi cao.

2) Prostaglandin G/H synthase 2 (COX 2) is a target that is inhibited by the topical drug salicylic acid and the biological etanercept.

The following compounds were identified by HIT as decreasing the expression level or activity of COX 2: ursolic acid, cinnamic acid (*aka* caffeic acid), hexadecanoic acid, lithospermic acid B (*aka* salvianolic acid B), linolenic acid, quercetin, berberine, kuraridin and isobutyrylshikonin.

The following two compounds were identified by HIT as increasing expression level or activity of COX 2: lauric acid and tigogenin.

The following 8 herbs contained compounds that were identified as down regulating COX 2: Bai hua she she cao, Di huang, Dan shen, Lu hui, Xi shu, Gong lao mu, Ku shen, Zi cao.

3) Prostaglandin G/H synthase 1 (COX 1) is a target that is inhibited by the topical drug salicylic acid.

The following compounds were identified by HIT as decreasing the expression level or activity of COX 1: ursolic acid, cinnamic acid (*aka* caffeic acid).

The following 4 herbs contained compounds that were identified as down regulating COX 1: Bai hua she she cao, Di huang, Dan shen and Zi cao.

4) Myeloperoxidase (MPO) is inhibited by the topical vitamin D analog calcipotriol.

The following compounds were identified by HIT as decreasing the expression level or activity of MPO: quercetin and berberine.

The following 2 herbs contained compounds that were identified as down regulating MPO: Xi shu and Gong lao mu.

5) Multidrug resistance protein 1 (ABCB1) is a substrate for salicyclic acid, prednisolone, methotrexate, alitretinoin and cyclosporine (which is also an inhibitor or inducer). The compound tryptanthrine was identied as an inhibitor. ABCB1 was identified as a target of camptothecin but the action was not available.

The following herb contained a compound that was identified as down regulating ABCB1:

Qing dai.

6) ATP-binding cassette sub-family G member 2 (ABCG2) is a substrate for methotrexate and is inhibited by cyclosporine. The compound quercetin was identified as increasing the expression level or activity of ABCG2 whereas berberine decreases expression level or activity. The action of camptothecin was not available.

The following herb contained a compound that was identified as down regulating ABC G2: Gong lao mu.

7) Aldo-keto reductase family 1 member C1 (AKR1C1) is inhibited by salicyclic acid. Of the componds identified for the herbs in HIT, salicyclic acid was one and it was listed as decreasing expression level or activity. In contrast cinnamic acid was identified as increasing expression level or activity.

The following herb contained a compound that was identified as down regulating AKR1C1: Qing dai.

8) Cytochrome P450 1A1 (CYP1A1) is inhibited by both clobetasol and methoxsalen.

The following compounds were listed as decreasing CYP1A1 expression level or activity: cinnamic acid (*aka* rosmarinic acid, caffeic acid), indirubin, berberine and isopimpinellin (*aka* limonin).

Tanshinone IIa was listed as up-regulating the gene while the reports for quercetin appeared contradictory including both inhibition and increasing expression.

The following 6 herbs contained compounds that were identified as down regulating CYP1A1: Di huang, Dan shen, Qing dai, Gong lao mu, Zi cao and She chuang zi.

9) Cytochrome P450 1A2 (CYP1A2) is inhibited by clobetasol, alitretinoin and methoxsalen.

Sucrose was identified by HIT as decreasing CYP1A2 expression level or activity and quercetin was identified as a direct inhibitor. Tanshinone IIa was identified as increasing expression level or activity.

The following 3 herbs contained compounds that were identified as down regulating CYP1A2: Qing dai, Xi shu and Lu hui.

10) Cytochrome P450 3A4 (CYP3A4) was identified by DrugBank as an enzyme target for the following APPs: calcitriol (substrate, inducer), fluticasone propionate (substrate, inhibitor), prednisolone (substrate, inhibitor), cyclosporine (substrate, inducer) and methoxsalen (substrate).

The compound obaculactone (*aka* limonin) was identified by HIT as directly inhibiting CYP3A4. Both tanshinone IIA and isopimpinellin were listed as up-regulating the gene. Quercetin was listed by HIT as decreasing expression level or activity as well as up-regulating the gene.

The following herb contained a compound that was identified as down regulating CYP3A4: Bai xian pi.

8.3.3.2 Comparison of target groupings, herbs and APPs

The targets COX 1 and COX 2 are involved in inflammation and are of direct relevance to psoriasis therapy (391). The following 8 herbs were all identified as potentially having inhibitory actions on at least one of these targets: Bai hua she she cao, Di huang, Dan shen, Lu hui, Xi shu, Gong lao mu, Ku shen and Zi cao. In this sense they have actions similar to those of the APPs etanercept, and salicylic acid.

TNF is a major target for psoriasis that is involved in inflammation as well as multiple processes including apoptosis, proliferation and immunoregulation (381, 392, 393). The following 9 herbs were all identified as down regulating TNF: Bai hua she she cao, Di huang, Dan shen, Lu hui, Qing dai, Xi shu, Gong lao mu, Ku shen and Zi cao. In this sense they are similar to the APPs golimumab and etanercept.

The targets ABCB1 (Multidrug resistance protein 1) and ABCG2 (ATP-binding cassette sub-family G member 2) are closely related proteins that are known to be involved in the transport of xenobiotics, including drugs, across cell membranes (394). These targets do not appear to be of direct relevance to psoriasis.

MPO (Myeloperoxidase) is an enzyme involved in phagocytosis, transcriptional

misregulation in cancer, atherosclerotic plaques and inflammation in cardiovascular disease (395-397). Its relevance to psoriasis is unclear.

Enzymes in the CYP 450 super family are well known for their roles in drug metabolism (398). They are also involved in skin responses to xenobiotics as well as in the metabolism of endogenous substrates including vitamins A and D. Since CYPs are up-regulated in psoriasis, the use of CYP inhibitors has been proposed as a strategy in psoriasis drug development (399, 400).

8.3.3.3 Comparison of herbs, species and APPs

For each of the herbs and their included species, a comparison was undertaken to determine how many of the 12 APPs shared at least one target with the 12 herbs (see Table 8.2). The herb Xi shu (*Camptotheca acuminata*) was found to share targets with all of the 12 APPs. Dan shen (*Salvia miltiorrhiza*) shared targets with 10 APPs. The herbs Qing dai (species *Isatis indigotica*) and Gong lao mu (*Mahonia* species) shared targets with 8 of the APPs.

Lu hui (*Aloe vera*), She chuang zi (*Cnidium monnieri*) and Qing dai (species *Baphicacanthus cusia*) shared targets with 6 of the APPs. Zi cao (species *Lithospermum erythrorhizon*) and Di huang (*Rehmannia glutinosa*) shared targets with 5 of the APPs. Bai xian pi (*Dictamnus dasycarpus*) shared targets with 4 of the APPs. Ku shen (*Sophora flavescens*) and Bai hua she she cao (*Oldenlandia diffusa*) shared targets with 3 of the APPs. Bing pian (species *Dryobalanops aromatica*) did not share a target with any of the APPs.

In cases where there are multiple species included under one herb there was considerable variation in the number of targets identified, but it is likely that this was due mainly to the relatively larger number of research reports that cited the main species.

Table 8.2 Identification of the APP-like herbs (*Oldenlandia diffusa,Rehmannia glutinosa, R. glutinosa var. purpurea, Salvia miltiorrhiza, S. miltiorrhiza f. alba, S. sinica, S. przewalskii var. mandarinorum, Aloe vera, A. vera var. chinensis, A. spp., A. ferox, Camptotheca acuminata, Mahonia aqulifolium, M. shenii, M. veitchiorum, M. japonica, M. bealei, M. fortunei, M. eurybracteata, M. bealei, M. gracilipes, M. fortunei, M. bodinieri, Sophora flavescens, Onosma paniculatum, O. hookeri, Arnebia guttata, A. euchroma, Lithospermum erythrorhizon, Cnidium monnieri, Dictamnus dasycarpus, Dryobalanops aromatica, Isatis indigotica, I. tinctoria, Baphicacanthus cusiaStrobilanthes formosanus*)

Species	**Chinese name**	**alitretinoin**	**calcipotriol**	**calcitriol**	**clobetasol**	**cyclosporine**	**etanercept**	**fluticasone propionate**	**golimumab**	**MTX**	**prednisolone**	**salicyclic acid**	**methoxsalen**	**no. of APPs**
O. diffusa	白花蛇舌草						√		√			√		3
R. glutinosa	干地黄				√		√		√			√	√	5
R. glutinosa	熟地黄													
R. glutinosa	鲜地黄(生地)													
R. glutinosa var. purpurea	紫地黄													
S. miltiorrhiza f. alba	白花丹参													
S. miltiorrhiza	丹参	√		√	√	√	√	√	√		√	√	√	10
S. sinica	拟丹参	√		√	√	√		√	√		√		√	8
S. przewalskii var. mandarinorum	紫丹参	√		√	√	√		√	√		√		√	8
A. vera var. chinensis	斑纹芦荟						√					√		2
A. spp.	多种芦荟提取物													
A. ferox	好望角芦荟													

A. vera	芦荟(库拉索芦荟)	√			√		√		√			√	√	6
C. acuminata	喜树	√	√	√	√	√	√	√	√	√	√	√	√	12
M. shenii	城口十大功劳		√		√	√	√		√	√		√	√	8
M. veitchiorum	川滇十大功劳		√		√	√	√		√	√		√	√	8
M. japonica	华南功劳木		√		√	√	√		√	√		√	√	8
M. japonica	华南功劳叶													
M. japonica	华南功劳子													
M. bealei	十大功劳叶												√	1
M. fortunei	细叶功劳叶					√				√				2
M. aqulifolium	尖叶十大功劳													
M. eurybracteata	宽苞十大功劳		√		√	√	√		√	√		√	√	8
M. bealei	十大功劳木		√		√	√	√		√	√		√		7
M. bealei	十大功劳叶													
M. bealei	十大功劳子													
M. gracilipes	细柄十大功劳		√		√	√	√		√	√		√	√	8
M. fortunei	细叶功劳木		√		√		√		√			√	√	6
M. fortunei	细叶功劳叶													
M. bodinieri	小果十大功劳		√		√	√	√		√	√		√	√	8
S. flavescens .	苦参						√		√			√		3
S. flavescens .	苦参实													
O. paniculatum	滇紫草													

A. guttata	假紫草													
O. hookeri	细花滇紫草													
A. euchroma	新藏假紫草													
L. erythrorhizon	紫草				√		√		√			√	√	5
C. monnieri	蛇床子			√	√	√		√			√		√	6
D. dasycarpus	白鲜皮			√		√		√			√			4
D. aromatica	冰片													
I. indigotica	板蓝根	√			√	√				√	√	√		6
I. indigotica	大青叶	√			√	√	√		√	√	√	√		8
I. tinctoria	欧州菘蓝	√				√				√	√	√		5
B. cusia	马蓝根	√			√	√				√	√	√		6
B. cusia	马蓝叶													
S.formosanus	台湾马蓝				√									1

8.3.3.4 APPs that share targets with the herbs

The number of targets that the different APPs were found to share with the 12 herbs ranged from 0 to 10. Fig. 8.5 indicates that the biologicals golimumab and etanercept and the topical salicylic acid shared targets with nine of the herbs while the herbs *Camptotheca* (Xi shu) and *Salvia* (Dan shen) shared targets with 12 of the APPs.

Since the above figure included the cytochromes which are mainly associated with metabolism of the drugs, these targets were removed from the comparison. As a result two herbs, *Cnidium* (Shi chuang zi) and *Dictamnus* (Bai xian pi), were removed from the matrix but the list of APPs was not affected. Consequently, the following 9 herbs: Dan shen (*Salvia miltiorrhiza* etc), Lu hui (*Aloe vera* etc), Qing dai (*Indigo naturalis*), Xi shu (*Camptotheca acuminata*), Gong lao mu *(Mahonia aquifolium etc),* Ku shen (*Sophora flavescens*), and Zi cao (*Lithospermum erythrorhizon, Arnebia* spp) Dan shen (*Salvia miltiorrhiza, S. sinica*), Di huang (*Rehmannia glutinosa*), Bai hua she she cao (*Oldenlandia diffusa*), Lu hui (*Aloe vera, A. ferox*), Qing dai (*Indigo naturalis*), Xi shu (*Camptotheca acuminata*), Gong lao mu (*Mahonia spp*), Ku shen (*Sophora flavescens*) and Zi cao (*Lithospermum erythrorhizon, Arnebia spp*) were considered to be 'APP-like' (Fig. 8.6).

The commonly used drug acitretin which appeared in many of the clinical trials in the systematic reviews (chapters 5-6) and was frequently combined with the HMs shared no targets with any of the shortlisted herbs and does not appear to be metabolized by the same enzymes as metabolise the compounds contained in the herbs.

APPs (drugs)	the corresponding herbs with the same therapeutic target(s)								
calcipotriol	*Camptotheca*	*Mahonia*							
MTX	*Camptotheca*	*Mahonia*	*Indigo*						
alitretinoin	*Camptotheca*	*Salvia*	*Indigo*	*Aloe*					
calcitriol	*Camptotheca*	*Salvia*	*Cnidium*	*Dictamnus*					
F.P.	*Camptotheca*	*Salvia*	*Cnidium*	*Dictamnus*					
prednisolone	*Camptotheca*	*Salvia*	*Cnidium*	*Dictamnus*	*Indigo*				
cyclosporine	*Camptotheca*	*Salvia*	*Cnidium*	*Dictamnus*	*Indigo*	*Mahonia*			
methoxsalen	*Camptotheca*	*Salvia*	*Cnidium*	*Lithospermum*	*Rehmannia*	*Mahonia*	*Aloe*		
clobetasol	*Camptotheca*	*Salvia*	*Cnidium*	*Lithospermum*	*Rehmannia*	*Mahonia*	*Aloe*	*Indigo*	
golimumab	*Camptotheca*	*Salvia*	*Oldenlandia*	*Lithospermum*	*Rehmannia*	*Mahonia*	*Aloe*	*Indigo*	*Sophora*
S.A.	*Camptotheca*	*Salvia*	*Oldenlandia*	*Lithospermum*	*Rehmannia*	*Mahonia*	*Aloe*	*Indigo*	*Sophora*
etanercept	*Camptotheca*	*Salvia*	*Oldenlandia*	*Lithospermum*	*Rehmannia*	*Mahonia*	*Aloe*	*Indigo*	*Sophora*

F.P.: fluticasone propionate; S.A.: salicyclic acid

Fig. 8.5 APP drugs and the corresponding herbs with the same therapeutic targets (including CYP 450)

APPs (drugs)	the corresponding herbs with the same therapeutic target(s)								
calcipotriol	*Camptotheca*	*Mahonia*							
calcitriol	*Camptotheca*	*Salvia*							
F.P.	*Camptotheca*	*Salvia*							
MTX	*Camptotheca*	*Mahonia*	*Indigo*						
prednisolone	*Camptotheca*	*Salvia*	*Indigo*						
alitretinoin	*Camptotheca*	*Salvia*	*Indigo*	*Aloe*					
cyclosporine	*Camptotheca*	*Salvia*	*Mahonia*	*Indigo*					
methoxsalen	*Camptotheca*	*Salvia*	*Mahonia*	*Aloe*	*Lithospermum*	*Rehmannia*			
clobetasol	*Camptotheca*	*Salvia*	*Mahonia*	*Aloe*	*Lithospermum*	*Rehmannia*	*Indigo*		
S.A.	*Camptotheca*	*Salvia*	*Mahonia*	*Aloe*	*Lithospermum*	*Rehmannia*	*Indigo*	*Oldenlandia*	*Sophora*
golimumab	*Camptotheca*	*Salvia*	*Mahonia*	*Aloe*	*Lithospermum*	*Rehmannia*	*Indigo*	*Oldenlandia*	*Sophora*
etanercept	*Camptotheca*	*Salvia*	*Mahonia*	*Aloe*	*Lithospermum*	*Rehmannia*	*Indigo*	*Oldenlandia*	*Sophora*

F.P.: fluticasone propionate; S.A.: salicyclic acid

Fig. 8.6 APP drugs and the corresponding herbs with the same therapeutic targets (excluding CYP 450)

8.3.4 Analysis of the pathways associated with biological targets of herbs using PANTHER

In total, the searches of HIT located 350 biological targets that were linked to the 12 candidate herbs. It was impractical to search every target in every herb so the following four herbs were selected for analysis with PANTHER.

Dan shen (Salvia) and Xi shu (Camptotheca) shared targets with the largest numbers of APPs so these appeared promising for further investigation. Moreover, Dan shen is used internally whereas Xi shu is used topically. Di huang (Rehmannia) was selected as it is very frequently used in the clinical trials in internal formulae while Qing dai (Indigo) was selected as it was commonly used in the clinical trials as a topical preparation. This provided a sample that included both topical and oral herbs.

Although Gong lao mu (Mahonia) was also used frequently as a topical medicine in the clinical trials, its targets are almost all focused on the compound berberine, which has already received considerable research attention regarding its actions and targets (321, 322, 324, 401). Therefore it was excluded.

In addition, analyses were conducted in PANTHER for etanercept and salicylic acid which are APPs that shared targets with multiple herbs including the four used in the PANTHER searches. The analysis was not limited to the targets that the herbs had in common with the APPs since it appeared likely that these herbs may act upon additional targets. In the previous investigation using DrugBank, targets of likely relevance to psoriasis were identified but there is, as yet, no complete listing of targets of relevance to psoriasis, therefore it was possible that the filtering of targets based on DrugBank results could exclude targets of relevance to psoriasis. Consequently, filtering was not used in this investigation.

For each herb, all targets for all species of the herbs which had been identified using HIT, were entered into PANTHER. The PANTHER Section II results were recorded. This section returned results on the following five aspects relating to the proteins: cellular component, protein class, molecular function, biological process, and pathway. Each of these results is reported below with a focus on the pathways. A few targets returned no results. The results for gene analysis are not reported.

8.3.4.1 Results of PANTHER analyses

The full lists of PANTHER Section II results are tabulated in Appendix 14-18. The main results are reported below for each herb. Pathways were short-listed based on the number of targets per pathway in descending order of frequency.

1) Results for Dan shen (*Salvia miltiorrhiza* and other *S.* species)

109 targets were identified by HIT for Dan shen, of which 102 were suitable to PANTHER. These returned the following main results for protein class in descending frequency of hits: hydrolase (24), enzyme modulator (19), signaling molecule (18), protease (15), transferase (15), receptor (15) and kinase (13).

The main molecular functions were: binding (51), catalytic activity (47), enzyme regulator activity (17), and receptor activity (16).

The main Biological Processes involved were: cellular process (62), metabolic process (59), cell communication (50), immune system process (36), apoptosis (27), response to stimulus (26), cell cycle (25), developmental process (22), transport (14) and system process (14).

In total 59 pathways were identified. The most frequently identified pathways, based on the number of targets per pathway, were as follows:

- Apoptosis signaling pathway (22)
- Angiogenesis (18)
- Gonadotropin releasing hormone receptor pathway (17)
- Inflammation mediated by chemokine and cytokine signaling pathway (15)
- Endothelin signaling pathway (12)
- Huntington disease (11)
- VEGF signaling pathway (11)
- Wnt signaling pathway (10) and
- EGF receptor signaling pathway (10).

Appendix 18 lists all the pathways along with the percentage of the targets included in each pathway, for example 21.8% of the targets of Dan shen were associated with the Apoptosis signaling pathway.

2) Results for Xi shu (*Camptotheca acuminata*)

143 targets were identified by HIT for Xi shu, of which 136 were suitable for analysis in PANTHER. These returned the following main results for protein class, in descending frequency of hits: nucleic acid binding (27), transcription factor (26), signaling molecule (25), receptor (24), transferase (20), hydrolase (20), enzyme modulator (18), oxidoreductase (16), kinase (14), protease (13) and extracellular matrix protein (10).

The main molecular functions were: binding (75), catalytic activity (61), transcription regulator activity (26), receptor activity (26) and enzyme regulator activity (15).

The main Biological Processes involved were: metabolic process (87), cellular process (85), cell communication (68), immune system process (58), response to stimulus (48), developmental process (33), cell cycle (32), apoptosis (28), reproduction (17), system process (13), cell adhesion (11) and transport (10).

In total 58 pathways were identified. The most frequently identified pathways, based on the number of targets per pathway, were as follows (see also Appendix 18):

- Gonadotropin releasing hormone receptor pathway (22)
- Angiogenesis (20)
- Apoptosis signaling pathway (18)
- Interleukin signaling pathway (18)
- Inflammation mediated by chemokine and cytokine signaling pathway (16)
- p53 pathway (13)
- VEGF signaling pathway (11)
- EGF receptor signaling pathway (10) and
- PDGF signaling pathway (10).

3) Results for Di huang (*Rehmannia glutinosa*)

The 100 targets identified by HIT for Di huang included 95 that were suitable for PANTHER. The anlaysis returned the following main results for protein class in descending frequency of hits: signaling molecule (20), transferase (17), oxidoreductase (15), hydrolase (13) and receptor (12).

The main molecular functions were: catalytic activity (49), binding (44) and receptor activity (13).

The main Biological Processes involved were: metabolic process (56), cellular process (53), cell communication (48), immune system process (44), response to stimulus (33), apoptosis (21), developmental process (16), transport (13) and cell cycle (11).

In total 56 pathways were identified. The most frequently identified pathways, based on the number of targets per pathway, were as follows (see also Appendix 18):

- Inflammation mediated by chemokine and cytokine signaling pathway (18)
- Apoptosis signaling pathway (15)
- Gonadotropin releasing hormone receptor pathway (15)
- Interleukin signaling pathway (13)
- Angiogenesis (11)
- T cell activation (11)
- B cell activation (9) and
- Huntington disease (8).

4) Results for Qing dai (*Indigo naturalis*)

46 targets were identified by HIT for Qing dai, of which 43 were suitable for PANTHER analysis. These returned the following main results for protein class in descending frequency of hits: hydrolase (13), transcription factor (8), signaling molecule (6), transferase (5), nucleic acid binding (5) and receptor (5).

The main molecular functions were: catalytic activity (26) and binding (18).

The main Biological Processes involved were: metabolic process (31), cellular process (20), immune system process (16), cell communication (15), apoptosis (12), response to stimulus (11) and developmental process (10).

In total 48 pathways were identified. The most frequently identified pathways, based on the number of targets per pathway, were as follows (Appendix 18):

- Apoptosis signaling pathway (11)

- Angiogenesis (7)
- Gonadotropin releasing hormone receptor pathway (7)
- Inflammation mediated by chemokine and cytokine signaling pathway (5)
- Huntington disease (5)
- PDGF signaling pathway (5)
- Interleukin signaling pathway (4) and
- FAS signaling pathway (4).

5) Results for salicylic acid

The 13 targets identified by DrugBank for salicylic acid were all suitable for PANTHER. They returned the following results for protein class in descending frequency of hits: transporter (8), transfer/carrier protein (6) and oxidoreductase (3).

The main molecular functions were: transporter activity (9) and catalytic activity (4).

The main Biological Processes involved were: localization (10), metabolic process (9), cellular process (6), multicellular organismal process (5) and immune system process (2).

In total 3 pathways were identified. These were as follows (Appendix 18):

- Inflammation mediated by chemokine and cytokine signaling pathway (2)
- Endothelin signaling pathway (1) and
- Toll receptor signaling pathway (1).

6) Results for etanercept

The 11 targets identified by DrugBank for etanercept were suitable to PANTHER. They returned the following results for protein class in descending frequency of hits: defense/immunity protein (10), receptor (6), cell adhesion molecule (5), extracellular matrix protein (3), signaling molecule (2), hydrolase (1), oxidoreductase (1), calcium-binding protein (1) and protease (1).

The main molecular functions were: receptor activity (8), binding (3), structural molecule activity (3) and catalytic activity (2).

The main Biological Processes involved were: immune system process (13), cellular process

(12), response to stimulus (12), developmental process (6), cellular component organization or biogenesis (3), apoptotic process (3), biological adhesion (3), metabolic process (2), reproduction (1) and biological regulation (1).

In total 5 pathways were identified. These were as follows (Appendix 18):

- Apoptosis signaling pathway (3)
- Inflammation mediated by chemokine and cytokine signaling pathway (2)
- Wnt signaling pathway (1)
- Endothelin signaling pathway (1) and
- Toll receptor signaling pathway (1).

8.3.4.2 Main pathways identified for the four herbs

The following four pathways were the most frequently identified pathways for Dan shen and Qing dai and they appeared in the top ten most frequently identified pathways in each of the four herbs:

- Inflammation mediated by chemokine and cytokine signaling pathway,
- Gonadotropin releasing hormone receptor pathway,
- Apoptosis signaling pathway, and
- Angiogenesis.

Interleukin signaling pathway appeared on the short list for three of the herbs (Xi shu, Qing dai and Di huang) and was lower on the list for Dan shen.

One of these four pathways, Inflammation mediated by chemokine and cytokine signaling pathway, appeared on the short list for all the four herbs and the two APPs. Apoptosis signaling pathway appeared for all four herbs and for etanercept but not for salicylic acid.

Conversely, Endothelin signaling pathway and Toll receptor signaling pathway appeared for both APPs. For the herbs, Endothelin signaling pathway was prominent for Dan shen. It did not appear on the short lists above for the other herbs but this pathway was present on the longer lists for Di huang, Xi shu and Qing dai. Similarly, Toll receptor signaling pathway appeared on the longer lists of pathways for Dan shen, Xi shu, Di huang and Qing dai. There was a similar result for the Wnt signaling pathway which appeared on the longer pathways

lists for all four herbs.

The following results are for the four most frequently identified pathways above plus the Interleukin signaling pathway. For each pathway, the targets that were common to multiple herbs are reported. Following this, the targets known to be relevant to psoriasis and/or inflammation, proliferation and angiogensis are short-listed in tabular format together with the associated herbs and compounds.

1) Inflammation

The Inflammation mediated by chemokine and cytokine signaling pathway involved 58 proteins in PANTHER with no repetitions due to the accession number issues identified below, rather, proteins tended to be grouped into families thereby underestimating the total number of proteins involved. The herb Di huang was associated with 17 targets, Xi shu with 16, Dan shen with 14 and Qing dai was associated with 8 protein targets. The targets that were associated with all four herbs were AP-1 [activator protein-1] *aka* c-Jun, EMC [ExtraCellular matrix protein], p65 *aka* NFkappaB, and PKC family. The following targets were each associated with three of the herbs: AKT, CHK [Chemokine aka C-C motif chemokine family], COX [Cyclooxygenase], IkappaB [Inhibitor of kappa light chain gene enhancer in B cells], Lipoxygenase [Arachidonate 5-lipoxygenase], MAPK [Mitogen-activated protein kinase family], PTEN [Phosphatase and tensin homologue] and STAT [Signal transducer and activator of transcription family]. INFgamma [Interferon gamma] was a target of Qing dai and Xi shu while IL2 [Interleukin-2] was identified for Di huang and Xi shu, as was IKK [Inhibitor of kappa-B kinase].

2) Gonadotropin releasing hormone receptor

The Gonadotropin releasing hormone receptor pathway is particularly complex and involves 216 protein components in PANTHER. It should be noted that this number is somewhat inflated since it is based on PANTHER accession numbers and what is basically the same protein or protein family can appear under different accession numbers. This phenomenon also occurs in the other pathways but it is comparatively infrequent. The herb Xi shu was associated with 31 proteins, Dan shen with 25, Di huang with 18 and Qing dai was associated with 14. The following proteins were associated with all four herbs: TGFbeta [Transforming growth factor beta], PKCs, p65 and Junc *aka* c-Jun [Transcription factor

AP-1]. The following proteins were each associated with three of the herbs: AKT, c-fos, COX2, ERK1/2 [Mitogen-activated protein kinase 1/3], FOS, JNK1/2 [Mitogen-activated protein kinase 1/2] and PPARalpha/gamma [Peroxisome proliferator-activated receptor alpha/gamma]. It should be noted that while TGFbeta appeared in this pathway, it is also associated with proliferation and is also located in a separate TGF-beta signaling pathway in PANTHER. Similarly, EGF [Pro-epidermal growth factor] and EGFR [Epidermal growth factor receptor] are targets of Xi shu which are located in this pathway but they are also associated with proliferation and differentiation. None of the herbs was associated with GnRHR [Gonadotropin-releasing hormone receptor], FSHbeta [Follitropin subunit beta] LHbeta [Luteinizing hormone beta] or GR [Glucocorticoid receptor].

3) Apoptosis

The Apoptosis signaling pathway involves 72 proteins (402). Dan shen was associated with a total of 21 targets and Xi shu was associated with 18, Di huang with 16 and Qing dai with 12. The protein targets that appeared repeatedly for all the four herbs were: TNF, p65 [NFkappaB], PKCs [Protein kinase C family], ATF [Activating transcription factor], c-Jun [Transcription factor AP-1], Caspases 3, 8 and 9, Bax and Bcl-2. In the case of etanercept, TNF was the only target identified. Protein targets identified for three of the herbs were IkappaB, MAPK family, AKT [RAC-alpha serine/threonine-protein kinase] and Fos [Proto-oncogene c-Fos].

4) Angiogenesis

The Angiogenesis pathway included 77 components in PANTHER. The herb Xi shu was associated with 16 of the protein targets in the pathway, the herb Dan shen was associated with 14 targets, Di huang with 10 targets and Qing dai was associated with 6 targets. The proteins identified for all four herbs were PKC [Protein kinase C family], c-Jun, and Caspase 9 all of which were common to the Apoptosis signaling pathway. Proteins identified for three herbs included AKT, c-Fos [c-Fos Transcription Factor], eNOS, and Erk [Extracellular regulated kinase]. The protein VEGF was identified for Dan shen and Xi shu and its receptor VEGFR-2 was located for Dan shen. Other proteins that are typical of angiogenesis, such as Ang-1 and 2 [Angiopoietin-1, 2], PDGF [Platelet-Derived Growth Factor] and FGF [Fibroblast Growth Factor] returned no results. It should be noted that the Wnt signaling pathway in PANTHER shares many proteins with the Angiogenesis pathway including: Wnt

[Wingless-type MMTV integration site family member], Fzd [Frizzled], Dsh [Dishelvelled], Axin, APC [Adenomatous polyposis coli protein], and GSK3 [Glycogen synthase kinase 3], all of which are involved in signal transduction through the cell wall. Of these proteins, results were returned for GSK3 alone which was associated with Xi shi and Qing dai.

5) Interleukins

The Interleukin signaling pathway involves 36 components in PANTHER. None of these were known targets of the two APPs. For the herbs, Xi shu was known to target 11 components, Dan shen targeted 8 components, Di huang targeted 7, while Qing dai targeted 4 components. All herbs targeted at least some interleukins which were all grouped together in PANTHER so this tended to underestimate the number of proteins included in this pathway. The interleukins associated with the herbs including IL-1A, IL-1B, IL-2, IL-4, IL-6, IL-8, and IL-10, with IL-6 and IL-10 being the most common. The proteins associated with three herbs included: ERK, c-fos, PKB [Protein kinase B], eNOS, p21CIP1 [Cyclin-dependent kinase inhibitor 1A] and STAT family. The STAT family proteins were targeted by Dan shen, Xi shu and Di huang. The same three herbs also targeted p21, p21CIP1, eNOS and PKB. Xi shu and Di huang also targeted IKK.

6) Targets not included in the above five pathways

Some of the frequently identified targets of the herbs did not appear in the above five pathways. These included CCNDI [G1/S-specific cyclin-D1] which is involved in Cell-cycle and appears in multiple pathways in PANTHER including Cell cycle and Wnt signaling pathway. CRP [C-reactive protein] which is involved in inflammatory processes and was associated with 12 pathways in PANTHER including the Endothelin signaling pathway but not with any of the five pathways discussed above.

ICAM1 [intercellular adhesion molecule 1], which is part of the immunoglobulin superfamily and is involved in immune response and inflammation, appeared as a frequent target for Dan shen, Ku shen and Bai hua she she cao but it did not locate any pathway in PANTHER. In KEGG, ICAM1 is located in the NF-kappaB signaling pathway and associated with lymphocyte adhesion and T-cell costimulation and is also in the TNF signaling pathway where it is associated with cell adhesion (403, 404).

8.3.4.3 Main pathways identified for the two APPs

Although etanercept and salicylic acid are not from the same class of drug, the three pathways identified for salicylic acid were also identified for etanercept. In the case of salicylic acid, the three pathways were all identified based on the involvement of its target COX 2, whereas another target COX 1 was only involved in the Inflammation mediated by chemokine and cytokine signaling pathway in PANTHER. No pathways were identified for any of the other targets identified in DrugBank. For etanercept, COX 2 is a target, so it identified the same three pathways. The main target, TNF is involved in the Apoptosis signaling pathway and in the Toll receptor and Wnt signaling pathways. Of the other targets identified by DrugBank, Lymphotoxin-alpha and Tumour necrosis factor receptor superfamily member 1B are both from the TNF family and are associated with the Apoptosis signaling pathway in PANTHER. Hence, three targets were primarily responsible for the PANTHER pathway results for these two APPs.

8.4 Summary and discussion of results

8.4.1 Targets of the herbs

The database searches identified numerous targets for the compounds included in the 12 herbs. In some cases, these targets had been investigated by the experiments discussed in Chapter 7 but in other cases the results found in this chapter were additional. The following targets show potential relevance to psoriasis for the main herbs.

In the case of Bai hua she she cao (*Oldenlandia diffusa*), many of the targets identified via HIT were also identified in Chapter 7 based on the searches of experimental studies. Most targets were associated with ursolic acid. Targets relating to apoptosis included Bax protein/Bcl-2, TNF, p21, and caspases 3 and 9 (393, 405-407). Targets associated with inflammation included COX-2, TNF, and Interleukin 6 (381, 391, 408). Targets such as iNOS and NF-kappa-B are involved in multiple processes including inflammation (381, 408).

For Di huang (*Rehmannia glutinosa*), targets identified in both chapters 7 and 8 included those related to inflammation including IL6, COX1 & 2, TNF-alpa, NFkappa B and PGE2. Chapter 7 targets tended to focus on inflammation with involvement of IL6 as well as RAGE

(*aka* AGER). Chapter 8 identified multiple interleukins (IL2, 4, 5, 6, 8, 10) and also targets associated with apoptosis including Caspases 3, 8 & 9, TNF, Bax and Bcl-2 (393, 406-408).

The targets identified in Chapter 7 for Dan shen (*Salvia miltiorrhiza*) were mostly concerned with apoptosis and proliferation. These included Caspases 3, 8, 9, Apoptosis regulator BAX, TNF, ERK2 and PARP. Inflammation related targets included IL1b, IL6, NF kappa B and TNF alpha. In addition, p38 is thought to be related to stress. In the broader search in Chapter 8, similar results were found but numerous additional targets of the compounds found in Dan shen were also identified. These included COX 1 & 2 for inflammation, VEGF-A for angiogenesis, targets related to vascular function, including endothelin-1 and ACTA2, and targets relating to immune function such as ICAM1 and VCAM1 (408-413).

A number of the targets that were identified for Ku shen (*Sophora flavescens*) in the experiments in chapter 7 also appeared in the Chapter 8 searches including Caspase-3, Interleukin-6, TNF, COX-2, NFkappaB and ICAM1. In addition, the chapter 8 searches located IL 4 and other targets related to inflammation and proliferation including AP-1, FOS and PPARG.

The main compound in the various species used as Zi cao (*Lithospermum erythrorhizon*, *Arnebia spp*) was shikonin. It was the main focus of the experimental studies in chapter 7 and returned the majority of the targets in chapter 8. In both chapters 7 and 8, targets associated with its actions on apoptosis included Caspase-3, TNF and Bcl-2, while the additional targets BBC6, AKT1 and p53 were identified in the Chapter 8 searches. Targets relating to inflammation that were identified in both chapters 7 and 8 included TNF, NF-kappa B, P53, COX 1 & 2 as well as the interleukins 1B, 6, 8, and 10. In chapter 8, targets relating to angiogenesis also were identified including VEGFR2 and TEK.

The targets identified for the compounds contained in Lu hui (*Aloe spp*) mainly related to inflammation, such as the Interleukins 1beta, 6, 8 and 10, COX 2, NF kappa B and TNF. Others related to apoptosis including Caspase 3, TNK and Bcl-2. In addition, COL1A1 was associated with collagen production and tissue repair.

For the compounds identified from the species used in the production of Qing dai (*Isatis, Baphicacanthus* and *Strobilanthes spp*), targets included those associated with inflammation such as IL4 &10, TNF and NF kappa B as well as a number of targets associated with

apoptosis such as Caspases 3, 8 and 9, TNF, Bax, Bcl-2, CDKN3, and with proliferation including AP-1, IFN gamma and PRKCA.

The main targets of Xi shu (*Camptotheca acuminata*) were mostly those related to the actions of quercetin and camptothecin. Apoptosis related targets included Caspases 3, 8 and 9, TNF, Bax, Bcl-2 and Ap1. Targets related to inflammation included the Interleukins 1A/B, 2, 6, 8, and 10, COX 1 & 2, NF kappa B and TNF. The main target relating to angiogenesis was VEGF-A. In addition, there were a number of targets relating to oxidative damage including catalase and superoxide dismutase. Other targets included those relating to DNA, notably TOP1 and TOP2A.

For Gong lao mu (*Mahonia spp*), despite the number of species included, the targets were dominated by those of berberine which occurs in all the species. Apoptosis related targets included BAX, Bcl2, TNF, Caspases 3, 8 & 9, BID and AP-1. Targets associated with proliferation included CCND1, PDGFA, IFN gamma and MAPK1 while VEGF-A is associated with angiogenesis and PDGFA is important in wound healing. Targets relating to inflammation included NF kappa B, NFKBIA, COX-2, Interleukins 4, 6 & 8 and TNF.

Overall, targets relating to inflammation and apoptosis tended to dominate the results. To what extent this indicates that the herbs are focused on these processes is difficult to determine. It is likely that the commonly found targets reflect the focus of past researches into these herbs. Since much natural products research is concerned with cancers and with chronic inflammation, targets assocated with these types of disease are likely to have high frequencies in data sets.

8.4.2 Targets of the herbs and APPS

Twelve APPs shared targets with the herbs and 11 of the 12 herbs shared at least one target with the APPs. It should be noted that acetretin did not share any targets with the herbs. Of the ten shared targets, the following were of most relevance to psoriasis therapy: COX 1 & 2 and TNF. The Cytochrome P 450 members 1A1, 1A2 and 3A4 appear to mainly be relevant to the potential for interactions between the herbs and APPs (391, 398, 399, 414, 415).

COX 1 and/or COX 2 were inhibited by compounds contained in the following 8 herbs: Bai hua she she cao, Di huang, Dan shen, Lu hui, Xi shu, Gong lao mu, Ku shen and Zi cao. This

indicated that these herbs had potential anti-inflammatory actions via COX 1 and/or 2. TNF was inhibited by compounds found in Bai hua she she cao, Di huang, Dan shen, Lu hui, Qing dai, Xi shu, Gong lao mu, Ku shen and Zi cao. Therefore each of these may exert an effect on TNF that could result in inhibition of the inflammatory and/or proliferative processes in which TNF is involved.

Since these herbs shared therapeutic targets with the APPs etanercept, golimumab and/or salicylic acid, they were considered to have APP-like actions.

8.4.3 Main pathways and proteins

The following four pathways were the top four pathways for Dan shen and Qing dai and they appeared in the top ten most frequently identified pathways in each of the four herbs: Apoptosis signaling pathway, Angiogenesis, Gonadotropin releasing hormone receptor pathway, and Inflammation mediated by chemokine and cytokine signaling pathway (Table 8.3-8.7).

The first of these pathways was also notable for the APP etanercept while both etanercept and salicylic acid had targets that were included in the Inflammation mediated by chemokine and cytokine signaling pathway.

It was not practicable to discuss each of the targets identified in each of the four pathways. Therefore, for the purpose of discussion, the main targets were selected based on being identified for multiple herbs and being known to be involved in processes of direct relevence to psoriaisis.

It is important to note that these targets have not necessarily been investgated in the context of psoriasis. They are ‘main’ in the sense of the database results and having received research attention. It is possible that the actual clinical effects reported for the herbs may have been due to effects on other less-studied targets and these may have been exerted by less-studied compounds and/or by compounds that do not as-yet appear in the databases.

The main targets are tabulated below for each of the four pathways together with the compounds that have been reported to act upon these targets. Since the same target may appear in multiple pathways, these are not discussed in each instance.

Table 8.3 Apoptosis pathway: main targets of the four herbs

Target	Herb	Compound & its regulating effect on the target
Bax	Dan shen/丹参	Ursolic acid ↑
	Qing dai/青黛	Lupeol ↑ , β-Sitosterol ↑ / ↓
	Xi shu/喜树	Hyperin ↓ , Quercetin ↑ / ↓
Bcl-2	Dan shen/丹参	Salvianolic acid A ↓ , Tanshinone IIa ↓
	Qing dai/青黛	Hexadecanoic acid ↓ , Lupeol ↓ , β-Sitosterol ↓
	Xi shu/喜树	Quercetin ↑ / ↓
Caspase 3	Di huang/地黄	Catalpol ↓ , Cinnamic acid ↓ , Stigmasterol ↑ , Succinic acid ↑ / ↓
	Dan shen/丹参	Dihydrotanshinone I ↑ , Lithospermic acid B ↓ , Salvianolic acid A ↑ /B ↓ , Tanshinone IIa ↓ , Ursolic acid ↑ / ↓
	Qing dai/青黛	Lupeol ↑ , Tryptanthrine ↑ , β-Sitosterol ↑
	Xi shu/喜树	Hyperin ↓ , Quercetin ↑ / ↓
Caspase 8	Di huang/地黄	Stigmasterol ↑
	Dan shen/丹参	Ursolic acid ↑
	Qing dai/青黛	β-Sitosterol ↑
	Xi shu/喜树	Quercetin ↑
Caspase 9	Di huang/地黄	Stigmasterol ↑
	Dan shen/丹参	Dihydrotanshinone I ↑ , Ursolic acid ↑
	Qing dai/青黛	Lupeol ↑ , β-Sitosterol ↑
	Xi shu/喜树	Quercetin ↑
Ikk	Di huang/地黄	Cinnamic acid ↓
	Xi shu/喜树	Quercetin ↓
NFkappaB/p65	Di huang/地黄	Aucubin ↓ , Cinnamic acid ↓ , Hexadecanoic acid ↓ , Lauric acid ↑
	Dan shen/丹参	Cryptotanshinone ↓ , Danshensu ↓ , Lithospermic acid B ↓ , Salvianolic acid B ↓ , Tanshinone IIa ↓ , Ursolic acid ↑ / ↓
	Qing dai/青黛	Salicylic acid ↓
	Xi shu/喜树	Quercetin ↓
TNF	Di huang/地黄	Aucubin ↓ , Cinnamic acid ↓ , Hexadecanoic acid ↑
	Dan shen/丹参	Caffeic acid ↓ , Cryptotanshinone ↓ , Ursolic acid ↑ / ↓
	Qing dai/青黛	Hexadecanoic acid ↑
	Xi shu/喜树	Quercetin ↓

Bcl-2 family members regulate the permeability of the mitochondrial membrane and play key roles in cell survival and death (416). It has been reported that the pro-apoptotic protein Bax is underexpressed in psoriatic skin while the anti-apoptotic protein Bcl-2 is over-expressed (406, 417). Increased levels of Tumour protein p53 (p53) were also reported (417). Experimental studies on cancer cell-lines have shown that ursolic acid down-regulated the expression of Bcl-2 and Bcl-xL (418), increased Bax expression while decreasing Bcl-2 expression, activated Caspase-3 (256) and also down-regulated NF-kappaB (419). Quercetin was reported to increase Bax expression and induce apoptosis (420, 421), and also increase

expression of Bax and caspase-3 (421).

Besides these up-regulating effects on effector caspases such as Caspase 3, a number of compounds can have more up-stream effects on initiator caspases including Caspases 8 and 9. Choi *et al* 2000 reported that ursolic acid activated Caspase -1, -3, -8 and -9 (422) while in human colon cancer cells a dose dependent activation of Caspases 3, 8 and 9 was associated with reduced proliferation (423). Kim *et al* 2011 found that ursolic acid acted via both the mitochondrial death pathway (via Bcl-2) and the extrinsic death receptor pathway (via Fas, caspase 8, caspase 3 & PARP) (424).

NFkappaB is important in cell survival and its overactivity is associated with cell proliferation (425). In the classical IKK/NFkappaB signalling pathway, proinflammatory cytokines, including TNF-alpha and IL-1 beta, activate the Ikk complex resulting in NFkappaB release to the nucleus and the transcription of diverse genes which can suppress apoptosis. Hence the inhibition of NFkappaB activation has been strategy for reducing tumour growth (425, 426). However, the roles of NFkappaB are complex and it can also have a role in cell death via other pathways that involve cross-talk wth JNK (425).

Priyadarsini and Nagini (2012) investigated the effect of quercetin on reactive oxygen species (ROS) and NFkappaB in a hamster buccal pouch carcinogenesis model and reported that quercetin attenuated ROS generation which abrogated NFκB signalling by preventing phosphorylation and degradation of IκB, translocation of NFκB to the nucleus and consequent activation of target genes associated with proliferation and apoptosis evasion (427).

A number of the compounds known to be contained in the herbs have shown down regulating effects on TNF (such as quercetin, ursolic acid, cinnamic acid), NF-κB (such as quercetin, ursolic acid, cinnamic acid), and IKK (such as quercetin, cinnamic acid). However, these results are mainly based on cancer cell-lines. In the blood of healthy volunteers, quercetin dose-dependently inhibited *in vitro* lipopolysaccharide (LPS)-induced TNF-alpha production but it had no anti-inflammatory effect on normal blood (428).

In psoriasis, 10 weeks treatment with the TNF inhibitor etanercept produced a reduction in NF-κB, Bcl-2 and Bcl-xL expression in endothelial cells during treatment. This was associated with a positive clinical response in terms of PASI reduction (429). It is plausible that some of the above-mentioned natural compounds may be exerting pro-apoptotic actions

similar to those of etanercept in psoriasis.

Table 8.4 Angiogenesis pathway: main targets of the four herbs

Target	**Herb**	**Compound & its regulated effect**
Caspase 9	Di huang/地黄	Stigmasterol ↑
	Dan shen/丹参	Dihydrotanshinone I ↑ , Ursolic acid ↑
	Qing dai/青黛	Lupeol ↑ , β-Sitosterol ↑
	Xi shu/喜树	Quercetin ↑
VEGF	Dan shen/丹参	Lithospermic acid B ↓ , Salvianolic acid B ↑ / ↓ , Tanshinone I ↓ , Ursolic acid ↑ / ↓
	Xi shu/喜树	Quercetin ↑ / ↓

While VEGF is one of the primary growth factors that induces angiogenesis, the pro-apoptotic Caspase 9 has been shown to be an inhibitor, and increasing its expression has been employed as an anti-angiogeneic strategy (430). All four of the herbs contain compounds that have been reported to up-regulate Caspase 9.

APPs including infliximab and methotrexate have been reported to reduce angiogenesis and cell infiltration in psoriaisis and Avramidis *et al* (2010) reported that etanercept therapy reduced angiogenesis in the endothelial cells of psoriasis patients and reduced expression of VEGF (429). A number of the compounds contained in the herbs have been reported to inhibit VEGF including ursolic acid, salvianolic acid B and quercetin. Cao *et al* 2014 reported that in melanoma cells quercetin inhibited STAT 3 actividation which had a down-regulating effect on VEGF (431). Pratheeshkumar *et al* 2012 reported that quercetin inhibited microvessel sprouting, proliferation, migration, invasion and tube formation of endothelial cells in a rat aortic ring assay when used at non-toxic concentrations and that it suppressed VEGF induced phosphorylation of VEGF receptor 2 and their downstream protein kinases AKT and mTOR (432).

In the case of salvianolic acid B, there are reports of VEGF inhibition in U937 histiocytic lymphoma cells (433) but recent studies have focused on its role in cardiovascular disease. In cardiac fibroblasts, Wang *et al* 2011 investigated the effects of salvianolic acid B on cardiac remodeling and reported a down-regulatory effect on VEGF via MMP-9 (434). In each of these cases, the down-regulatory effects reported on VEGF involved upstream mechanisms rather than direct inhibition.

Table 8.5 Inflammation mediated by chemokine and cytokine signaling pathway: main targets of the four herbs

Target	Herb	Compound & its regulated effect
COX 1	Di huang/地黄	Cinnamic acid ↓
	Dan shen/丹参	Cinnamic acid ↓ , Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓
COX 2	Di huang/地黄	Cinnamic acid ↓ , Hexadecanoic acid ↓ , Lauric acid ↑
	Dan shen/丹参	Caffeic acid ↓ , Lithospermic acid B ↓ , Salvianolic acid B ↓ , Tigogenin ↑ , Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓
Ikk	Di huang/地黄	Cinnamic acid ↓
	Xi shu/喜树	Quercetin ↓
INF gamma	Qing dai/青黛	Indirubin ↓
	Xi shu/喜树	Quercetin ↓
NFkappaB/p65	Di huang/地黄	Aucubin ↓ , Cinnamic acid ↓ , Hexadecanoic acid ↓ , Lauric acid ↑
	Dan shen/丹参	Cryptotanshinone ↓ , Danshensu ↓ , Lithospermic acid B ↓ , Salvianolic acid B ↓ , Tanshinone IIa ↓ , Ursolic acid ↑ / ↓
	Qing dai/青黛	Salicylic acid ↓
	Xi shu/喜树	Quercetin ↓
STAT	Di huang/地黄	Cinnamic acid ↓
	Dan shen/丹参	Cryptotanshinone ↓ , Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓

The Inflammation mediated by chemokine and cytokine signaling pathway in PANTHER illustrates chemokine-induced adhesion and migration of leukocytes, which infiltrate to the tissue and the transcriptional activation which enables the recruitment of more leukocytes. From the therapeutic perspective, inhibition of specific chemokines and receptors within this pathway could prevent the excessive recruitment of leukocytes to sites of inflammation (402).

The cyclooxygenases Cox 1 and Cox 2 are targets of non-steroidal anti-inflammatory drugs including asprin and of a variety of natural products (208, 435). Hao *et al* 2009 investigated the actions of salvianolic acid B on neck squamous cell carcinoma models and found that it inhibited growth of tumour xenografts and reduced COX-2 expression (436). Kowalczyk *et al* 2013 investigated the effects of ursolic acid and other compounds in a skin carcinogenesis model in SENCAR mice. They reported that ursolic acid inhibited epidermal hyperplasia, reversed COX-2 mRNA levels and decreased IL-6 expression (437).

NFkappaB is involved in multiple signaling pathways including those associated with

inflammation, and the aberrant regulation of NFκB is involved in cancer development. NFκB is also involved in regulation of COX-2 and iNOS expression. Numerous natural products have been reported to inhibit NFkappaB (438). Quercetin has been reported to reduce the transcriptional activity of NFκB in human hepatocytes (439) and in primary human keratinocytes it suppressed lipopolysaccharide (LPS) induced NFkappaB activation (440).

In an ethanol induced oxidative stress rat model, the addition of quercetin decreased plasma levels of the pro-inflammatory cytokines TNF-alpha and INF-gamma and reduced ALT levels indicating anti-inflammatory and liver protective effects (441).

Table 8.6 Interleukin signaling pathway: main targets of the four herbs

Target	**Herb**	**Compound & its regulated effect**
Ikk	Di huang/地黄	Cinnamic acid ↓
	Xi shu/喜树	Quercetin ↓
IL-1	Dan shen/丹参	Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓
IL-6	Di huang/地黄	Hexadecanoic acid ↑ ,Aucubin ↓ , Lauric acid ↑ ,γ-Aminobutyric acid ↓
	Dan shen/丹参	Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓
IL-10	Di huang/地黄	Hexadecanoic acid ↑
	Qing dai/青黛	Hexadecanoic acid ↑
	Xi shu/喜树	Quercetin ↑ / ↓
STAT	Di huang/地黄	Cinnamic acid ↓
	Dan shen/丹参	Cryptotanshinone ↓ , Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓

Interleukins are cytokines that are secreted by some leukocytes and can act upon other leukocytes. The Interleukin signaling pathway in PANTHER describes how they can mediate different biological responses via activation of a combination of different signal transduction pathways, including the Jak-STAT, ERK, and PI3K-PKB pathways (402).

The IL-1 family has proinflammatory effects while IL-10 is an anti-inflammatory cytokine and IL-6 can have both pro- and anti-inflammatory effects. In B16F-10 melanoma cells, treatment with ursolic acid was found to down regulate gene expression of TNF-alpha, IL-1beta and IL-6 and to promote Caspase-3 mediated apoptosis (442). In diabetes mellitus model, quercetin reduced IL-1 beta-induced nitrite production, iNOS protein and also inhibited NF-κB activation but these effects were not found for its metabolites (443).

IL-10 inhibits synthesis of IL-1, IL-1b, TNF-a, IL-6 and IL-8 and can suppress the inflammatory response. In a reperfusion injury model in rats, quercetin treatment improved protection and increased the levels of both TNF-alpha and IL-10 (444).

A cell-based screen using hepatoma HepG2 cells found that quercetin can activate the JAK/STAT pathway (445). In a recent study of quercetin in cholangiocarcinoma (CCA) cells, activation of the JAK/STAT pathway by IL-6 and Interferon-gamma, was suppressed by pre-treatment with quercetin and the effects involved STAT1 and STAT3 (446). In diabetes-induced glomerular hypertrophy in mice, low dose ursolic acid markedly ameliorated deteriation and its actions were identified as via suppression of diabetes-induced activations of STAT-3, ERK1/2 and JNK pathways (447).

Table 8.7 Gonadotropin releasing hormone receptor pathway: main targets of the four herbs

Target	**Herb**	**Compound & its regulated effect**
COX 2	Di huang/地黄	Cinnamic acid ↓ , Hexadecanoic acid ↓ , Lauric acid ↑
	Dan shen/丹参	Caffeic acid ↓ , Lithospermic acid B ↓ , Salvianolic acid B ↓ , Tigogenin ↑ , Ursolic acid ↓
	Xi shu/喜树	Quercetin ↓
NFkappaB/p65	Di huang/地黄	Aucubin ↓ , Cinnamic acid ↓ , Hexadecanoic acid ↓ , Lauric acid ↑
	Dan shen/丹参	Cryptotanshinone ↓ , Danshensu ↓ , Lithospermic acid B ↓ , Salvianolic acid B ↓ , Tanshinone IIa ↓ , Ursolic acid ↑ / ↓
	Qing dai/青黛	Salicylic acid ↓
	Xi shu/喜树	Quercetin ↓
PPARalpha/gamma	Di huang/地黄	Caprylic acid ↑
	Xi shu/喜树	Quercetin ↓

The above components of the Gonadotropin releasing hormone receptor pathway are all involved in multiple pathways. Cox 2 and NFkappaB were mentioned above.

The peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that function as transcription factors and regulate the expression of genes. PPAR alpha is involved in skin homeostasis, the control of keratinocyte proliferation and differentiation. It contributes to wound healing and regulates skin inflammation. Its expression decreases in inflamed skin and PPAR-alpha activation has been reported to to reduce experimental skin inflammation. In wound healing, PPAR-alpha expression is upregulated in the keratinocytes at the edge of the wounded skin but then declines. Studies have suggested that PPAR-alpha

function may be altered in psoriasis (448). A recent micro-array analysis of psoriatic skin, found that PPAR-alpha was lower in lesional skin versus healthy skin (449).

A gene reporter assay found that quercetin inhibited the activation of PPAR-alpha, -beta and –gamma (450). Mulberry leaf-related extracts rich in quercetin were studied in human aortic endothelial cells and found to reduce expression of NFkappaB and activator protein (AP)-1, as well as increase PPAR-alpha and -gamma DNA binding (451).

Overall, many of studies that were included in HIT and many of the subsequent studies referred to above were not directly related to psoriasis and most were not focussed on the short-listed herbs but on specific compounds such as quercetin and ursolic acid which can also be contained in a variety of other plants. Therefore, the database results cannot provide definitive indications of how the herbs might act on the various pathways, rather, they provide clues as to how the compounds contained in the herbs may act singly and in combinations, thereby these results can assist in the planning of studies that focus more directly on psoriasis and its associated processes.

8.4.4 Comparison with results of other studies of targets in psoriasis using *in silico* methods

In order to investigate the mechanisms of psoriasis, Lu *et al* 2013 employed DNA micro-arrays and *in silico* methods to analyse multiple transcription factors. Skin biopsy samples from 21 normal healthy donors and 33 patients with plaque type psoriasis were used to create the micro-array. Differentially expressed genes (DEGs) were identified and those with significant fold changes were included in the *in silico* analysis. Data were obtained from the TRANSFAC database (www.gene-regulation.com) and the Transcriptional Regulatory Element Database (TRED) to determine the relationships between genes and transcription factors, and pathways were identified using KEGG. They located large numbers of KEGG pathways including Leukocyte transendothelial migration, Cell adhesion molecules, PPAR signaling pathway, Cell cycle, Toll-like receptor (TLR) signaling pathway and steroid hormone biosynthesis. Transcription factors noted as significant by the authors included Jun proto-oncogene (JUN, c-Jun), Signal transducer and activator of transcription 1 (STAT1) and NF-kappaB (452).

Since PANTHER was used in this study rather than KEGG, there is no one-to-one correspondence between pathways. While Cell cycle and TLR were not pathways at the top

of the frequency lists in this project, TLR was identified as relevant to all the 4 herbs with Cell cycle appearing for Di huang, Xi shu and Dan shen (see Appendix 18). Of the targets, NF-kappaB was a target of Di huang, Xi shu, Qing dai and Dan shen, the STATs were targets of Di huang, Xi shu and Dan shen with STAT1 being located for Di huang in the Angiogenesis pathway in PANTHER. All four of the herbs in the pathway analysis showed hits for c-Jun and it's associate Transcription factor AP-1. In the PANTHER analysis, c-Jun was associated with the Apoptosis and Angiogenesis pathways but AP-1 was related to the Inflammation pathway.

Lu *et al* 2014 analysed the urine of psoriaisis sufferers who were being successfully treated with Optimized Yinxieling formula, which comprised seven herbs, using High Performance Liquid Chromatography (HPLC) and Mass spectrometry and compared the results with those from normal subjects. They used *in silico* metabolomics to identify potential biomarkers and protein targets. Nine targets were reported: Peptidyl-prolyl cis-trans isomerase A (PPIA), MAP kinase p38 (MAPK12), Cytosolic phospholipase A2 (PLA2), Integrin alpha-L (LFA-1), Integrin beta-3 (ITGB3), E selectin, 92 kDa type IV collagenase (MMP-9), Low affinity immunoglobulin gamma Fc region receptor II-a (FCGR2A), and Purine nucleoside phosphorylase (PNP) (378). Only the herb Zi cao was common to Optimized Yinxieling formula and to our list of 12 herbs.

These proteins were not high frequency items in our search. We retrieved results for other other MAPKs but not for MAPK12. In PANTHER this protein was located in 12 pathways including Gonadotropin-releasing hormone receptor pathway. PLA2 is included in three of our frequently located pathways, Angiogenesis, Inflammation mediated by chemokine and cytokine signaling pathway, and Gonadotropin-releasing hormone receptor pathway but there were no hits for the 12 herbs. Low affinity immunoglobulin gamma Fc region receptor II-a (FCGR2A) is one of the targets of etanercept in DrugBank but its actions are 'unknown', no pathway was located in PANTHER and no herbs were located in HIT. Results were, however, returned for E-selectin which is listed in HIT as a target of ursolic acid, quercetin and vitamin E which are components of the short-listed herbs Bai hua she she cao, Dan shen, Xi shu and Lu hui. Integrin beta-3 (ITGB3) was a target of tanshinone IIa in Dan shen and is located in the Inflammation mediated by chemokine and cytokine signaling pathway. 92 kDa type IV collagenase [*aka* Matrix metalloproteinase-9] (MMP-9) is a target of ursolic acid, tanshinone IIa, quercetin, apigenin, emodin and rottlerin (in Bai hua she she cao, Dan shen,

Xi shu, Lu hui) and is located in the Alzheimer disease-presenilin pathway and the Plasminogen activating cascade in PANTHER.

Although there was only one herb in common between the formula used by Lu *et al* 2014 and our list, there were still some commonalities between the targets found in both analyses. Notable were targets relating to inflammation and compounds contained in the herbs Bai hua she she cao, Dan shen, Xi shu and Lu hui. No results were returned for Zi cao which is a herb commonly used in psoriaisis. Considering the considerable differences between the study by Lu *et al* and this study, similar results could hardly be expected. What this comparison does illustrate is the potential for target level analysis to be used to explore the possible effects of combinations of herbs that are used in clinical settings.

For the herb Sheng di huang (*Rehmannia glutinosa*), Jiang *et al* 2013 undertook an *in silico* analysis of the molecular network of genes that are related to psoriasis using a number of sources and databases to identify the active compounds in the herb and their targets (using http://pubchem.ncbi.nlm.nih.gov/) as well the genes of relevance to psoriasis (using http://www.ncbi.nlm.nih.gov/gene). This data was analysed in IPA (Ingenuity Pathway Analysis). The authors reported that the following protein targets were common to both the herb and psoriasis: Tumor protein p53 (TP53 *aka* p53), NF-kappaB, TNF and Matrix metalloproteinase-1 & 2 (MMP1 & 2). They identified the NF-kappaB signaling pathway as common to psoriasis and the herb sheng di huang. Glycogen synthase kinase 3-beta (GSK3B aka GSK3beta) was identified as the primary target via which the herb acts upon the NF-kappaB signaling pathway (376).

Di huang was one of the 4 herbs for which the pathways were investigated in the present study. HIT did not identify p53 as a target of Di huang although it was found for a number of the other herbs (including Zi cao, Xi shu, Dan shen) but NF-kappaB and TNF were identified as targets of Di huang as well as targets of other herbs. Neither MMP1 nor MMP1 were identified as targets of Di huang in HIT but MMP9 was identified as a target of numerous herbs. GSK3 was identified as a target of Qing dai and Xi shu but not of Di huang and was located in the Interleukin and Gonadotropin releasing pathways in PANTHER. These differences in results may be due to differences in the lists of compounds identified for Di huang which has a complex composition as well the different databases used. These issues remain challenges for development of *in silico* methods.

Chapter 9: General discussion and future directions

9.1 Summary of the project

This project aimed to investigate the clinical effects of HMs on psoriasis vulgaris (chapters 5 & 6) and to explore the possible actions of the herbs that showed the most promise of efficacy in the clinical studies (chapters 7 & 8). The following sections discuss the approaches used, their main findings and their limitations, as well as propose future directions for research and implications for practice.

9.1.1 The approach to the analysis of clinical and experimental studies

In order to investigate the clinical trial evidence for herbal therapies for psoriasis, a methodological approach was used that adopted the Cochrane collaboration methods for systematically reviewing the RCT literature and undertaking meta-analyses of outcome measures and adapted these methods to the specific features of herbal therapies that may be applied topically or administered orally and may be composed of a single herb or multiple herbs.

This modified approach also considered which herbs appeared in multiple studies and undertook pooling of data on this basis where possible (see Chapters 5-6 and publications (135, 157-159)). This approach enabled the identification of herbs for which there was greater or lesser evidence of clinical efficacy.

A safety analysis was also undertaken based on the reported adverse events. It found that these were mainly associated with local stimulation from the topical herbal medicine and tended to be tolerated (212, 214, 215, 219). When herbs showed evidence of poor safety profiles they were not considered as candidates for further analysis, for example Lei gong teng (see chapter 5).

This approach to reviewing the clinical research literature also considered the results of experimental studies when framing discussions of how the HMs may act in the alleviation of psoriasis symptoms and signs (see chapter 7 and publications (135, 157-159)). These studies suggest that certain of the herbs used in the clinical trials have actions that may modify inflammatory processes and can affect cell proliferation. Since both of these processes are

involved in psoriasis, it appeared possible that a least some of the reported clinical benefits for the use of these HMs were due to anti-inflammatory and/or anti-proliferative effects of compounds contained within the plants from which the herbal medicines were made.

By adapting the methods of the systematic review and meta-analysis of randomised controlled trials to the specific characteristics of herbal therapy, it was possible to arrive at assessments of the best available evidence for topical and oral herbal medicine use in psoriasis vulgaris. Moreover, by synthesising these results with those from published experimental studies, it was possible to identify herbs for which there was corroborating evidence of pharmaceutical actions that are relevant to psoriasis therapy.

9.1.2 The selection of herbs for further analysis

The outcomes found in the experimental studies provided indirect evidence of effects of relevance to psoriasis therapy (see chapter 7), but the mechanisms that underlie the development of psoriasis remain as-yet incompletely understood (34). In addition, most of the experimental studies on the HMs used *in vitro* and *in vivo* models that are not specific to psoriasis with many being focussed on atopic dermatitis and on cancers (see chapter 7). Consequently it was difficult to locate experimental evidence that was of direct relevance to herbal therapy for psoriasis. Nevertheless, a number of the *in vivo* and *in vitro* studies reported that the herbs had effects on therapeutic targets such as COX and TNF that are known to be relevant to conventional pharmacotherapy in psoriasis. This finding in chapter 7 led to the exploration of other methods for further investigating the outcomes of the systematic reviews that focussed on therapeutic targets.

One option was to extend the searches of the biomedical databases to focus upon specific therapeutic targets and specific compounds that were contained in the herbs. An alternate approach was to develop a method and procedures for utilizing the resources available via on-line databases. Considering the rising importance of on-line databases in research, the second option was selected (453, 454). This multi-stage *in silico* method is described in Chapter 8 along with the results of the analyses.

This approach used clinical evidence for anti-psoriatic effects combined with acceptable safety and experimental evidence of at least some biological activity of relevance to psoriasis as the basis for selection of a short list of herbs for further work (Fig. 9.1). The

resultant list of 12 herbs included those that were used internally: *Oldenlandia diffusa*, *Rehmannia glutinosa* and *Salvia miltiorrhiza*; and herbs that were used topically: *Aloe vera*, *Indigo naturalis*, *Camptotheca acuminata*, *Mahonia aquifolium*, *Sophora flavescens*, *Lithospermum erythrorhizon*, *Cnidium monnieri*, *Dictamnus dasycarpus* and borneol. However, each of the herbs in the topical group could also be used orally in traditional practice so the whole group was examined together. These twelve herbs formed the promising candidates for further exploration of their potential 'APP-like' properties.

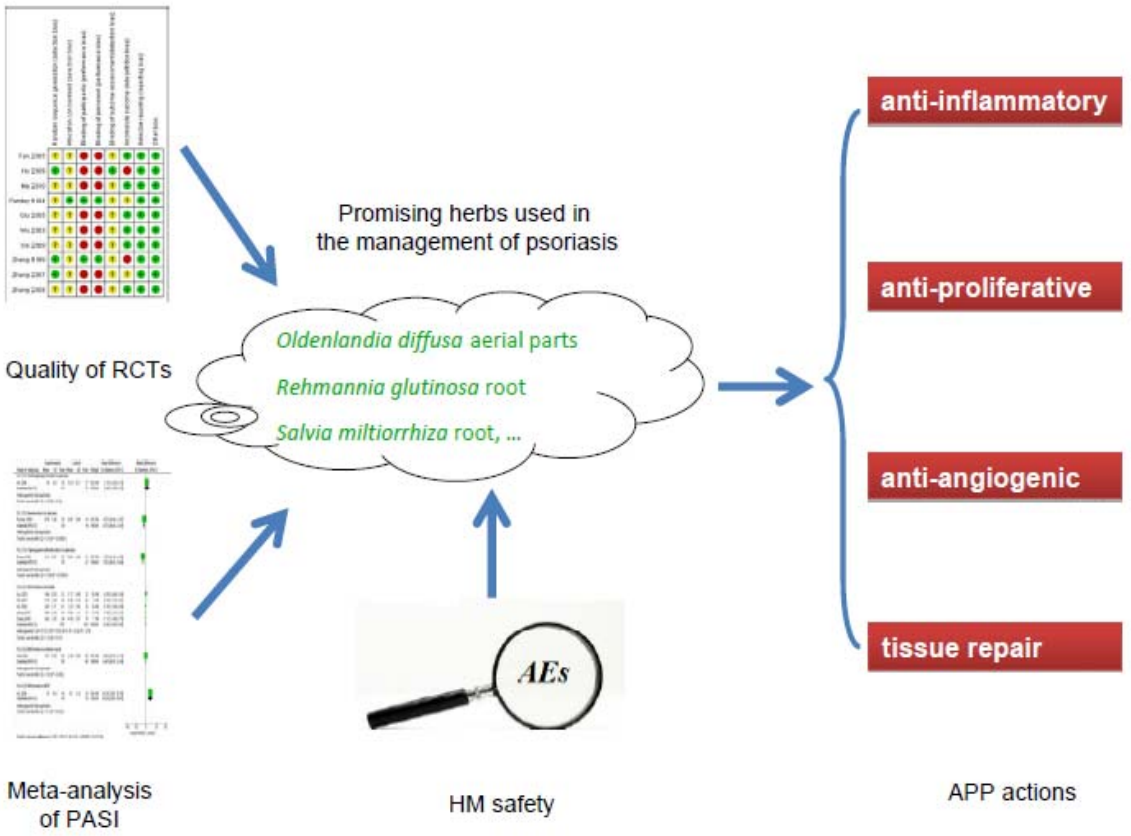

Fig.9.1 Diagram of the process for selection of herbs for *in silico* screening based on analysis of clinical trials

An advantage of this approach to identifying herbs for further research is that each has shown an acceptable safety profile in humans combined with potential clinical efficacy. A limitation is the top herbs were selected principally on the basis of frequency of occurrence in trials, many of which used multi-herb formulae. It does not necessarily follow that the herb that appears more frequently in formulae for which efficacy is reported, is more efficacious than a herb used less frequently. The current state of the RCT data for psoriasis is limited so the above list of herbs cannot be considered complete as a list of herbs

efficacious for psoriasis or as including the most effective herbs. What the list does provide is the herbs for which there are multiple sources of clinical and experimental evidence.

It should be noted that in this project frequency of occurrence was not interpreted as evidence of efficacy, importance or significance. Frequency was used as a broad gauge of confidence in the reported result since the result appears multiple times. However repetition of a result does not necessarily indicate the result is accurate. Frequency is also used as a means of limiting the search space when it is not possible to consider all the available data. In a more comprehensive investigation, all herbs that showed potential efficacy could be included.

9.2 The *in silico* approach to the analyses of herbal medicines in psoriasis

Just as the methods used for conducting systematic reviews utilise resources that are broadly available to researchers via online platforms, it was decided that the approach taken in this project to the analysis of targets should use resources that are available to a broad range of researchers. Moreover, the approach should be adaptable to disorders other than psoriasis. Hence the databases HIT, DrugBank and PANTHER were selected (386, 388-390, 402) and all three were used in combination (Fig.9.2).

It needs to be noted that the method presented in this project remains under development and the procedures used still suffer from limitations which it is expected can be improved in future iterations of these methods and procedures. It should also be noted that the results for the pathways represent a pilot study which is based on a limited number of herbs and does not cover all the pathways identified.

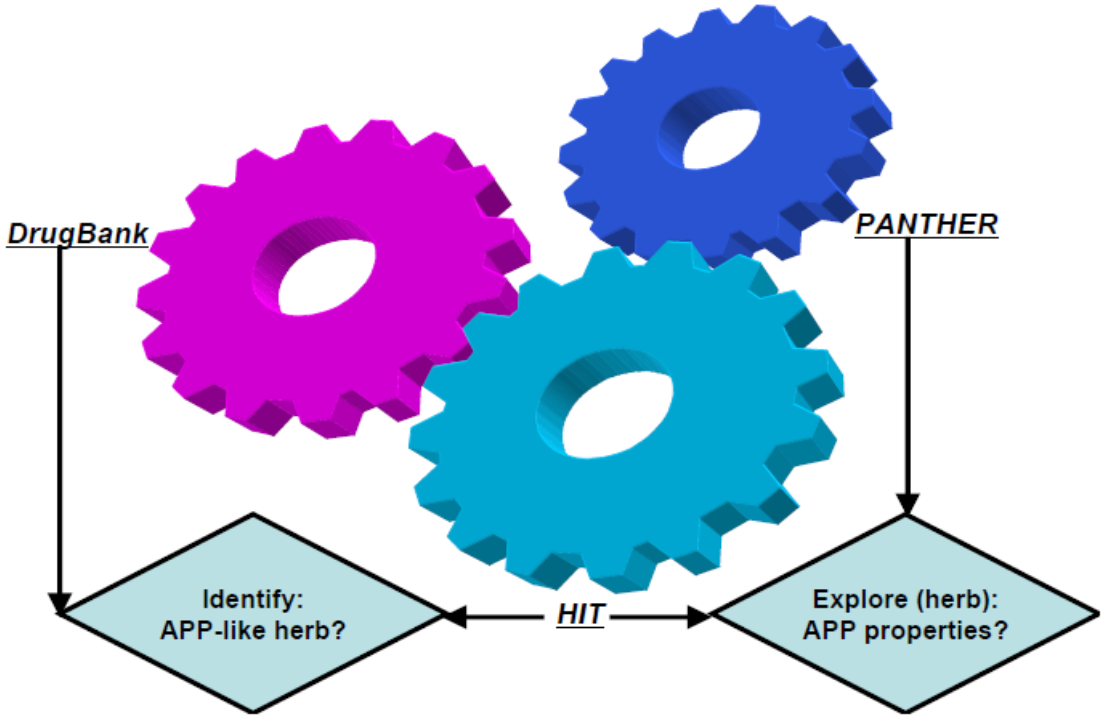

Fig.9.2 Conceptual diagram of the target-directed *in silico* analysis

9.2.1 Identifying the targets of the herbs

Although a number of purpose-built databases of relevance to natural products research have be reported in the literature (383, 455, 456), these are not all broadly available. Of the on-line databases examined, only HIT combined the features of herbal names, species names, compounds, therapeutic targets and had free access (386). Major advantages of HIT as a primary platform were that it is a curated database that has been updated relatively recently and is based on a range of resources including books and published research reports. It has links to other online resources including Uniprot and KEGG which can assist in identifying target proteins and in cross-referencing the multitudinous names and acronyms by which they are known. HIT also contains botanical names for plants and Chinese names in both Pin yin and Chinese characters which makes this database of particular relevance to Chinese herbal medicine research.

As a result of conducting trial searches using HIT it became evident that the lists of compounds contained in particular herbs were not always complete. Consequently, when using a herb name as the basis for undertaking a search in HIT, certain compounds known to be contained in the herb were not located. For example, the herb Bai hua she she cao is

known to contain ursolic acid but this compound was not listed for this herb in HIT although the compound is listed elsewhere in HIT. To compensate for this this shortcoming, the recently published *Encyclopaedia of TCM* was used to develop more comprehensive lists of compounds for the herbs and these compound names were used as inputs to HIT rather than the herb names. While this approach resulted in a more complete identification of targets, this aspect of the *in silico* method still suffers the following limitations. A number of the compounds that have been identified as components in herbs are not included in HIT and consequently could not retrieve any targets. In addition, compounds did not necessarily identify all the targets that have been reported in the literature. Since this is likely to have been due to either the literature being excluded in the curation process or the database awaiting an update, there was no apparent method of remediating this shortcoming beyond attempting supplementary literature searches or adding other databases of herb compounds and targets such as CHEM-TCM [http://chemtcm.com/], and TCMGeneDIT [http:// http://tcm.lifescience.ntu.edu.tw/].

Searches of HIT can return a large number of targets particularly when multiple compounds are entered for a single herb. Consequently, certain targets may appear repeatedly in searches as a result of being identified by different compounds in the same herb or by being identified by different species used as that herb (see Chapter 8). The 482 compounds identified 350 biological targets. Full lists appear in Appendix 1-12. In the results for herbs in Chapter 8, the targets that appeared more frequently were generally considered as the main targets of the herb for the purposes of reporting a short list of targets but frequency of occurrence is not necessarily related to the therapeutic importance of the target. Therefore frequency alone was not the only criterion for target selection and targets of known relevance to biological processes of relevance to psoriasis were also retrieved.

9.2.2 Identifying targets of relevance to psoriasis

Since the herbs are not specific for psoriasis and are thought to have activity in multiple diseases, the issue of which targets are more relevant to psoriasis arose. There was also the issue of whether these targets were suitable for pharmacoptherapy. One option was to examine the literature to obtain the best evidence and expert opinion on druggable targets for psoriasis (34, 372, 457). This was done but in the interest of developing a more generally applicable method, it was decided to employ the database DrugBank to identify targets that were highly likely to be relevant to psoriasis (388, 390).

The approach taken to using DrugBank was to identify the known therapeutic targets of each of the APPs that had been approved for the management of psoriasis. It was reasoned that at least some of the targets of these drugs would be of direct relevance to psoriasis. Consequently, the consolidated list of targets of the APPS could be used to refine the target lists identified via HIT. This approach could also be used to further limit the short list of herbs by excluding those that shared no targets with any of the APPs.

In general, the searches of DrugBank found relatively fewer targets of the APPs than were found for the herbs via HIT. A principal reason for this was most of the herbs contained multiple compounds whereas the APPs were single purified compounds. It is also probable that different criteria were used when compiling lists of targets in HIT than were used in DrugBank and that neither database is comprehensive. Nevertheless the following nine of the shortlisted herbs were found to share at least one target with an APP: Dan shen (*Salvia miltiorrhiza, S. sinica*), Di huang (*Rehmannia glutinosa*), Bai hua she she cao (*Oldenlandia diffusa*), Lu hui (*Aloe vera, A. ferox*), Qing dai (*Indigo naturalis*), Xi shu (*Camptotheca acuminata*), Gong lao mu (*Mahonia spp*), Ku shen (*Sophora flavescens*) and Zi cao (*Lithospermum erythrorhizon, Arnebia spp*).

The relationship between the herbs and the APPs based on the presence or absence of targets in common was illustrated in Figs.8.5 and 8.6 which show that the greatest overlap between the herbs and APPs in terms of shared targets was for etanercept, golimumab and salicylic acid and this relationship held when the cytochromes were not considered. Conversely, the herbs Camptotheca (Xi shu) and Salvia (Dan shen) shared targets with the greatest number of APPs. However, having more targets in common does not equate with greater efficacy nor does sharing a target indicate that the herb necessarily has a similar action to the corresponding APP. These herbs were classified as 'APP-like', but this it is only from the viewpoint of target sharing and is not based on clinical efficacy. Also, some of the targets in common are of known relevance to psoriasis, others are of unclear relevance while others may be incidental inclusions of no relevance at all to psoriasis.

While these results should not be over-interpreted, this approach does provide a method for limiting the search space when presented with numerous targets. Also, there is the possibility that some of the targets of the APPs shared with the HMs that are currently not considered relevant to psoriasis may have an as-yet unknown role. Conversely, this approach is limited in that it excludes all targets of the herbs that were not listed under any APP, thereby limiting

the possibility of identifying new targets of relevance to psoriasis. Nevertheless, this approach could be considered for other herbs and for other diseases since it may provide clues to additional targets of relevance that may have not yet received research attention for the particular disease.

9.2.3 Identifying the pathways

The pathway investigation was limited to four of the nine herbs that shared targets with the APPs but the searches of PANTHER were based on full lists of the HIT targets for these herbs without any filtering for targets in common with the APPs. Therefore, this step was not dependent on searches of DrugBank, it used the results from the HIT/DrugBank synthesis to assist in limiting the number of herbs for consideration but contained the full lists of targets for the included herbs.

Since analysis of all the remaining 9 herbs was impractical, four herbs were selected primarily on the basis of sharing multiple targets with the APPs. As noted earlier, the frequency of targets should not be considered a measure of the potential importance of a herb and is not a primary component of this method. Since this project is essentially a pilot of the method, frequency was used for shortlisting items for investigation since it was impractical to analyse every item. On the other hand, the selection of herbs for which there were numerous results for targets overall, and these included targets in common with APPs, appeared likely to lead to meaningful results in the pathways analysis. Also, the adoption of frequency enabled an objective approach to generating lists of results.

When all targets were entered into PANTHER, numerous pathways were returned with each of the four herbs having targets that were involved in between 48 and 59 pathways. Not all of the targets identified by HIT were suitable for entry into PANTHER and there was considerable difference in the nomenclatures used by both databases, but after these issues had been resolved only a few of the HIT targets proved unproductive in PANTHER. This indicated that this aspect of the method was practicable once the interface issues were addressed.

Due to the large number of pathways identified, it was impractical to investigate all of them, so frequency was again adopted as an objective approach to shortlisting pathways for consideration. Even though the target lists had not been filtered for relevance to psoriasis, the

pathway results showed distinct relevance to psoriasis with the pathways that included the larger numbers of target proteins being those associated with apoptosis, inflammation, and angiogenesis. Surprisingly, the Gonadotropin-releasing hormone receptor pathway was frequently identified. However, this result was due to targets within this complex pathway also being involved in processes relevant to psoriasis including inflammation and proliferation rather than the herbs having effects on gonadotropin and related hormones. It is also likely that PANTHER pathways that contain large numbers of proteins (216 in Gonadotropin-releasing) tend to appear higher on the frequency lists than pathways with fewer items (e.g. 49 in Wnt signaling pathway) so this effect needs to be considered in future studies.

It is also important to note that pathways themselves are theoretical constructs. Their scope and their components vary according to the data source with the PANTHER pathways differing from those in KEGG. Although we consulted KEGG during this project, we did not attempt a pathway analysis using KEGG and do not have a view on which database is the more useful. Future studies may consider undertaking a comparative analysis using both PANTHER and KEGG.

9.3 Research questions and main results

The principal research questions and the main results of this research project were as follows:

1) What is the current state of the clinical evidence for the efficacy and safety of herbal medicine for psoriasis?

Based on the results of the systematic reviews of randomised controlled trials of psoriasis vulgaris there is promising evidence of efficacy in terms of PASI score reduction for the use of HMs singly and in formulations used topically or orally and for topical HMs used in combination with APPs. This evidence is based on multiple RCTs and these were grouped according to similar designs, test intervention and controls in order to enable data pooling (135, 157-159).

The strength of the clinical evidence is limited by the relatively short duration of the studies which typically lasted between one and three months and the lack of a follow-up in most studies. The use of PASI 50 and above as a criterion in the meta-analyses due to the different

ways in which the data were reported in different studies meant that although there was evidence of efficacy, this was based on a minimum threshold rather than on the higher PASI 75 which is reported for pharmaceuticals in contemporary studies.

Methodological inadequacies in reporting and in design, limited the quality of the evidence. Although all studies were designated as RCTs, in some studies there was inadequate description of the method of random allocation so it was unclear whether this aspect of the design was correctly implemented. While a number of the studies that compared single HMs with placebo were properly blinded, lack of blinding was an issue in many studies. It is difficult to design a placebo for a multi-ingredient decoction and when a HM in pill or capsule was compared with an APP the different appearances precluded blinding. To what extent this lack of blinding induced a bias in favour of the HM is difficult to ascertain but it remains a concern. In the case of studies that combined a HM with an APP, but only used the APP in the control arm, there is considerable potential for bias in favour of the combination therapy. Future studies using this design should always use a placebo for the HM in the control arm.

An additional source of possible bias is the publication of positive studies only, either as a result of institutional or commercial pressure, researcher bias or the preference of journals. Tests of publication bias were undertaken when there were sufficient numbers of studies available that used the same design and outcome (i.e. 10 or more) and these did not show evidence of publication bias but such tests were not possible for all comparisons so the possibility of such a bias remains.

In the case of the multi-herbal studies, variation in the ingredients of the herbal formula from study to study also limited the meaningfulness of data pooling although this issue was addressed where possible by grouping studies with ingredients in common. Also, within a study it is not always clear whether there was adequate control of the use of concomitant medications and whether their use was equivalent in both arms of the study. In studies that used treatment based on syndrome differentiation (TSD) and used modified formulae, the reported effects are not directly based on the primary formulation alone and this could introduce a source of uncontrolled variation. Another source of variation could be the quality of the herbal ingredients. This is less a concern in commercial products but the majority of the studies used locally prepared medications and most did not report data on quality control. This presents an issue when attempting to replicate the study.

In terms of safety, for the topical preparations there were reports of localised adverse events (AEs) but these were not serious and were reported to have been managed. In the oral HMs, serious AEs were not reported. However, the AE reporting was not adequate in all trials so the safety data remains incomplete. In the case of three of the herbs *T. wilfordii*, Neem and *Dictamnus dasycarpus*, serious AEs have been reported in the literature although none were reported in the included RCTs (135). This may have been due to the range of preparations of these herbs that have been used but caution is urged in the oral use of these herbs.

2) Which herbs and/or formulas have the best evidence of efficacy in the management of psoriasis?

Of the topical preparations, *Mahonia* (Gong lao mu), *Aloe vera* (Lu hui) and *Indigo naturalis* (Qing dai) have been evaluated in multiple trials and these trials included comparisons with placebo (159). *Camptotheca acuminata* (Xi shu) was compared with placebo in only one of the included RCTs but it has also been the subject of other clinical and experimental studies and has been in clinical use in China for decades. Most of these trials showed evidence of efficacy but data pooling was not feasible for all the studies so it is not possible to determine which of these herbs were more or less effective.

In the multi-ingredient topical herbal formulae, a number of herbs were used repeatedly with reported efficacy including *Sophora flavescens* (Ku shen), *Lithospermum erythrorhizon/ Arnebia* species (Zi cao), *Cnidium monnieri* (She chuang zi), *Dictamnus dasycarpus* (Bai xian pi), *Angelica dahurica* (Bai zhi), *Tribulus terrestris* (Bai ji li), *Biota orientalis* (Ce bei ye) and borneol (Bing pian). Of the herbs used in topical studies, Ku shen, Zi cao, Qing dai and Bai xian pi were also used the oral formulae used in multiple studies. However, the most frequently used herbs in the oral formulations were *Rehmannia glutinosa* (Di huang), *Salvia miltiorrhiza* (Dan shen) and *Oldenlandia diffusa* (Bai hua she she cao) (158).

Of the topical multi-ingredient HMs, only Liubai Baibi formula showed efficacy in more than one study (158) and each of the oral multi-ingredient HMs was only used in one RCT.

Based on the results of the RCTs, all of the above herbs showed promise of efficacy for the management of psoriasis vulgaris based on multiple trials employing the same herb and reporting clinical efficacy but it was not possible to determine which herb was more effective

than another and in the case of the multi-ingredient formulae it was not possible to determine whether the most commonly used herbs were the main contributors to the reported efficacy.

In terms of oral or topical use, all of the herbs used frequently in the topical preparations can also be used orally, so there was no clear distinction between oral and topical herbs. However, *Mahonia*, *Camptotheca* and *Aloe* were not components of the oral HMs. From the safety perspective, of the above herbs *Camptotheca* and *Dictamnus* appear safe when used topically but need to be used with caution as oral medications.

3) Which herbs show the best evidence of anti-psoriatic activity based on the combination of clinical and experimental studies?

There was considerable variation in the volume of experimental studies that have been published in English on the above listed herbs and their constituents. Evidence of activity of relevance to psoriasis was notable for the following herbs and compounds:

Ursolic acid which is a constituent of *O. diffusa* (Bai hua she she cao) and other plants has been the subject of multiple studies that have shown activity against inflammation, induction of apoptosis, and enhancement of epidermal barrier recovery. Indirubin from *Indigo naturalis* (Qing dai) has shown anti-inflammatory and anti-proliferative activity in multiple studies. Experimental studies of shikonin from *Lithospermum erythrorhizon* and *Arnebia* species (Zi cao) have reported anti-inflammatory, anti-proliferative and anti-angiogenic effects as well as benefits in wound healing. Berberine which is found in *Mahonia* species and in other plants has anti-inflammatory effects and *Mahonia* extracts have been reported to exert anti-mutagenic and anti-carcinogenic effects.

Sophora flavescens (Ku shen) and its constituent matrine have shown anti-inflammatory effects and extracts have been shown to induce apoptosis and to exert anti-pruritic effects. *Aloe vera* (Lu hui) extracts have been investigated for wound healing and anti-inflammatory effects, have shown anti-proliferative actions and have shown efficacy for pruritus. *Camptotheca* (Xi shu) extracts as well as the compound camptothecin have been shown to have anti-proliferative actions.

Rehmannia glutinosa (Di huang) and *Salvia miltiorrhiza* (Dan shen) extracts have both shown anti-inflammatory activity and anti-proliferative effects have also been reported for Dan shen and its constituent tanshinone IIA.

Few studies were located for *Dictamnus* (Bai xian pi), *Cnidium* (She chuang zi) and borneol but each has been reported to have effects of relevance to psoriasis with borneol also being known to promote the absorption of topical preparations.

This survey of the experimental literature was mainly based on sources listed in PubMed and was not comprehensive in that it did not consider every study on these herbs and their constituents, rather it focussed on studies of relevance to psoriasis in terms of models related to skin and/or actions of relevance to psoriasis. In order to undertake a comprehensive assessment of the experimental literature, a database would need to have been constructed. This was impractical so existing databases were used in the final component of this study.

4) What are the likely mechanisms of action of the most promising herbs and/or their constituents?

Based on current knowledge of psoriasis, it is evident that inflammatory and proliferative processes are involved, there must be a reversal of these in the recovery process, and wound healing processes are also involved. The experimental studies on the main herbs that were discussed in Chapter 7 indicated that numerous herbs could potentially reduce inflammation and reduce proliferation by inducing the apoptosis of keratinocytes. In addition, the experimental studies indicated that certain of the herbs, their extracts and/or compounds known to be contained in the herbs had measurable effects on proteins known to be involved in inflammation and/or proliferation such as COX 2, TNF, Caspase 3, Bax and others. This suggested possible mechanisms of action but the focus of Chapter 7 was on these processes, so the results were confirmatory more than exploratory.

In Chapter 8 a more objective approach was undertaken which used databases to explore the protein targets of the compounds contained in the 12 herbs for which there was clinical evidence of potential efficacy and there was evidence of activity of relevance to psoriasis based on *in vitro* and/or *in vivo* experimental studies. Although the process for selection of this list of herbs was somewhat subjective since there was no plausible way of ranking the herbs according to efficacy, the subsequent *in silico* analyses were more objective in that

they were based on the frequency of citation in the databases rather than a judgement regarding relevance to psoriasis.

The HIT analyses returned few targets for the herbs She chuang zi (*Cnidium monnieri*), Bai xian pi (*Dictamnus dasycarpus*) and Bing pian (borneol, *Dryobalanops aromatica*) but the other herbs were identified as potentially affecting many targets with Caspase-3 [CASP3], Apoptosis regulator Bcl-2 [BCL2], Apoptosis regulator BAX, tumour necrosis factor [TNF], Transcription factor p65 [NF kappa B] and prostaglandin G/H synthase 1 & 2 [COX-1 & 2] being frequently occurring proteins.

When the targets of the compounds contained in the herbs were compared with the targets of the APPs, which was a much more constrained list compared to herb-related targets, the proteins TNF, COX-1 and COX-2 were the main shared targets that were down-regulated by compounds in the herbs. This suggested a predominance of anti-inflammatory actions and effects of proliferation. However, based on the target list of the herbs it was also apparent that proteins relating to apoptosis were very frequent in the results returned from HIT.

To further explore the possible pathways via which the herbs may act, four herbs that had returned multiple results from HIT (Dan shen, Xi shu, Di huang and Qing dai), were analysed using PANTHER. The results indicated that each of these herbs could be affecting more than forty PANTHER pathways so it possible that their mechanisms of action are complex. Based purely on the frequency of involved proteins, the Apoptosis signaling pathway and the Angiogenesis pathway were notable. As expected, pathways associated with inflammation including the Inflammation mediated by chemokine and cytokine signaling pathway, Interleukin signaling pathway and sections of the Gonadotropin releasing hormone receptor pathway were also frequent occurrences.

What this analysis suggested was that besides anti-inflammatory effects, certain of the frequently used herbs may be exerting pro-apoptotic and anti-angiogenic effects. However, there was variation between the herbs in the numbers of targets identified so it was not possible to determine which pathways were of greater or lesser importance based on the frequency analysis or whether differences between the results for different herbs were indicative of their primary actions.

5) What are the implications of the clinical and research evidence for the clinical management of psoriasis and for ongoing research?

These aspects are discussed below.

9.4 Innovative aspects of the project

This novelty and innovation in this project included modifications to the systematic review process together with a novel approach to employing the outputs of systematic reviews of clinical studies as inputs to *in silico* analyses that are focussed on target proteins and the biological pathways in which they are situated. This approach has the potential to build bridges between the meta-analysis results derived from multiple clinical trials, the results of experimental studies and target-focussed drug discovery and development.

9.4.1 The use of results of SRs to select herbs for further investigation

The first component of this study employed conventional SR methods based on the Cochrane Handbook to select RCTs for inclusion, evaluate study quality and undertake meta-analyses of outcome measures, in particular of PASI. A point of innovation at this stage was the determination of which of the herbs in the multi-herbal formulae had been used repeatedly in different RCTs that had shown evidence of efficacy based on the meta-analysis results and also evidence of safety based on the results for AEs. This provided a rational approach to the short-listing of herbs for further consideration.

Another innovation to the SR approach was the addition of an investigation of how the shortlisted herbs might act in the management of psoriasis based on searches of the experimental literature on the effects of the short-listed herbs, their extracts and/or constituent compounds. This approach provided a bridge between the clinical research which frequently employed multi-herb formulations and the experimental research which typically focuses on an extract of a single herb or on a single compound.

Both of these additions to the general methodology used for SRs are adaptations to the needs of researchers and clinicians who require particular data regarding which herbs in a formula are of relevance to the disorder and which physiological effects these herbs could exert. This approach is not specific to psoriasis and could be adapted to SRs of multi-ingredient formulae for other disorders.

9.4.2 Target-directed large-scale analyses using multiple databases

The protein targets of a compound can imply the molecular mechanisms of its therapeutic actions and and also indicate its possible adverse effects. Targets also have pharmacogenetic implications for the discovery of drugs against specific conditions. However, the amount of the estimated potential targets on the human genome is huge (374). This suggests that database(s) should be employed to undertake large-scale data analyses of protein targets in an effort to understand how herbs, which can contain multiple compounds, and multi-ingredient formulae may act upon a particular disorder.

An innovative aspect of this project was the identification of the protein targets of each of the short-listed herbs using HIT based on the active compounds contained in the herbs, rather than the herb names themselves. This broadened the scope of the searches and ensured the inclusion of all potentially relevant data. This large scale approach allowed the use of frequency effects to identify targets for further consideration. While there are limitations to the use of frequency (discussed earlier and also below), this provides an objective approach to short-listing targets and has the potential to identify targets that may not have received attention for the specific disorder.

Another novelty of the *in silico* approach was the 'APP-like' herb identification and the herb/APP property exploration. This involved combining the results from the HIT database with the targets of the APPs derived from the DrugBank database which is based on FDA data. The results from DrugBank were used to filter the HIT data and the herb target lists that contained APP drug targets were identified to provide lists of the herbs that were 'APP-like'. This provided an approach to comparing herbs and pharmaceuticals that are employed for the same disorder in terms of their likely effects on specific proteins.

A further innovation was the use of the PANTHER database to process all the targets derived for a particular herb from HIT in order to generate frequency data for the molecular functions, biological processes, cellular components, protein classes and pathways via which the compounds in the herb could be acting. This provided an objective approach to organizing the complex data on targets into particular biological processes and enabled predictions as to which signaling pathways the herbs may affect. This approach may assist in understanding how multiple compounds may affect a biological process and may also be able to provide clues as to the biological mechanisms involved in imperfectly characterised diseases such as

psoriasis. An earlier study attempted an analogous approach for diabetes using a quite different method (458).

The use of the database cluster, HIT, DrugBank and PANTHER, can provide an objective and rapid approach to the identification of herb targets and the exploration of the possible pharmaceutical actions of multiple herbs in relation to a specific disease.

9.5 Implications for further experimental and clinical research in psoriasis

The results of the *in silico* analyses suggest that a number of the herbs can affect protein targets of relevance to psoriasis but these predictions require further examination via experimental and clinical studies.

The studies of HMs reported in chapter 7 and the targets of the HMs located in the database searches included proteins whose association with psoriasis has been well-established including TNF, COX, IFN-gamma and others (234, 259, 332). What was missing from the data were studies that reported on targets that have received more research in recent years including IL 17, IL-23 (459-461), JAK/STAT signalling members (462, 463), VEGF-A, Tie2 and other proteins relating to angiogenesis (409, 463) and adenosine receptor and other G protein related proteins (464). This illustrates how databases can become dated and require regular revision.

Since much of the data on the herbs is derived from cell-line studies and *in vivo* studies using models that are not directed at psoriasis, more focussed experimental studies are required. *In vitro* studies using human psoriatic keratinocytes and fibroblasts appear to closely model the psoriatic phenotype (465). In animals, old models such as the mouse tail model would appear still relevant for the preliminary testing of topical preparations (466, 467), while models such as Balb/C mice (468-470) and more recently developed psoriasis xenograft mouse models (463, 471) more closely model the clinical manifestations of psoriasis and would appear to be the models of choice in future studies. Such studies could up-date the literature with regard to the targets mentioned above and might consider measuring some of the targets identified in this project.

Clinical testing of the effects of promising herbs singly and in various combinations in psoriasis sufferers should be considered with the use of PASI and biomarkers as outcomes.

An example of this approach is a study by Song *et al* 2010 that employed multi-ingredient systemic and topical formulae in 15 participants and measured PASI as well as levels of psoriasis-associated antigen (Pso p27) in plaque biopsies (472). Reductions in both PASI and Pso p27 were reported but none of the herbs short listed in Chapter 8 were employed by Song *et al*. If such an approach were used, it is suggested that the herbal formula used should comprise few ingredients to as to make the results more interpretable. In addition to PASI, micro RNA (mRNA) biomarkers in serum could be employed as outcomes (457, 473) and serological measures of markers of inflammation, proliferation and other processes of relevance to the specific herbs could be measured to assess the effects of the herbs and shed light on the processes involved.

Prior to undertaking a clinical study of psoriasis using a herb or a herbal formula it is suggested that an *in silico* analysis be undertaken. Since most contemporary studies undertake chromatographic analysis of the test formula prior to the study, the results of this analysis could form the list of compounds entered into the *in silico* analysis. This should identify the potential targets and pathways via which the herbal medicine may act and can provide directions for the selection of appropriate serological tests and marker proteins as outcome measures.

In cases where participants are likely to be using conventional APPs in addition to the herbal therapy, the identification of which Cytokine p 540 is involved in the metabolism of the compounds contained in the herbal medicine would assist in the monitoring of the safety of the clinical trial and could assist in determining whether any of the AEs reported were due to the herbs and/or interactions with pharmaceuticals.

The finding that certain of the herbs shared targets with certain of the APPs also opens the possibility of the combination of herbal and APP drugs in a rational manner. Physicians could consider applying specific ‘APP-like’ herbs with definite therapeutic target(s) as replacements to the APP or to enable reduction in APP dosage in the case of drug resistance or AEs due to the APP. Clinical studies of such an approach could be considered.

9.6 Implications for herbal research and natural products drug discovery

As clinical herbal medicine moves more towards an evidence-based approach, analyses that can synthesise the outcomes of clinical trials and experimental studies are needed. There is,

however, a major disjunction between the approach used in clinical herbal medicine and that used in experimental studies. In general, *in vitro* and *in vivo* studies test extracts of single herbs, fractions of an extract or single compounds. This approach mirrors that of conventional drug discovery research in which a single compound that acts upon a particular target is sought. Also, compared with pharmaceuticals, plants tend to contain relatively low concentrations of each compound. In contrast, experimental studies tend to use higher concentrations of these compounds. So there exist a number of disjunctions between what is tested in experimental studies and what is used in clinical practice.

In contrast to experimental studies, clinical herbal medicine employs single or multiple herbs and consequently an array of compounds which potentially can act on multiple targets. In taking an evidence based approach, herbal therapy could move to the use of single herbs but in the case of Chinese medicine that would seem like a return to an approach that was used in ancient times prior to the advent of rationally constructed multi-herb formulae which has been the mainstay of professional practice for two millennia.

Fundamental to the concept of formula design in Chinese medicine is the notion that components of the formulae target components of the disease, with some components focusing on symptoms while others focus on underlying mechanisms. Some formulae focus almost wholly upon mechanism and can be used in any disease that shares this mechanism while other formulae are symptom focussed and are only applicable when the symptom presents. In practice, the formulae that are designed for a particular patient tend to combine both aspects and are modified as the symptoms change.

To date, it has been difficult to assess the effects of multi-herb formulae. The SR approach used in this study determined that the included multi-herb formulae produced clinical improvements in psoriasis that were not inferior to acetritin and these HMs appeared not to produce any severe adverse events. Also, it was possible to identify which individual herbs were likely to have contributed to this therapeutic effect but the SRs could not provide data on the mechanisms of action of these herbs.

Using future iterations of the *in silico* approach presented in this study it may be possible to identify all the targets of a formulae and locate these within pathways to investigate how the formula might act. In addition, this approach could be used to explore the possible effects of modification to a formula via the addition or subtraction of herbs. It is plausible that some

combinations of herbs may all be targeting the same proteins thereby compensating for the relatively low levels of the compounds contained in the herbs or their low bioavailability. As seen in the results, multiple herbs can contain the same compounds and different compounds can have the same targets. In addition, different compounds can target different proteins within the same pathway, so it is plausible that when this is happening smaller amounts of each of the compounds are needed to achieve a change in the pathway.

Currently, the *in silico* modelling of the actions of multi-herb formula is still in its infancy and this approach remains limited due to the paucity of data on the compounds contained in many of the herbs in use and their protein targets. In this study, rather than choose a single formula we selected herbs that have been used in multiple clinical studies singly or as components of formulae and have been the subject of experimental studies. As a result, the *in silico* analyses returned a considerable amount of data. This indicated that these herbs may have targeted multiple proteins and at least some of these proteins were included in pathways involved in apoptosis, inflammation and angiogenesis. However, had other less-studied herbs been used it is likely that few results would have been returned. So the results for a multi-herbal formula that contained more and less intensively studied herbs would likely be skewed and may over emphasise the role of the herbs for which there is more data. This possible effect would need to be considered when interpreting results.

Nevertheless, this approach could be used to explore combinations of herbs to determine whether they share the same targets or targets within the same pathway. Currently, the *in silico* approach used in this project is very time consuming to conduct and is limited by the available data, but the speed limitations could be overcome by the design of new software and the amount of data is continually increasing. Therefore, *in silico* methods similar to this could provide a new method for rational herbal formula construction in the future.

9.7 Future research directions

This combination of analyses of clinical trial data followed by large scale *in silico* analyses of the relationships between multiple compounds, multiple targets and multiple pathways could be applied to other complex diseases such as the cancers, cardiovascular diseases and nervous system diseases. In these diseases, the larger volume of clinical data is likely to provide more focussed sets of candidate herbs. Also, the higher volume of data on the targets

and pathways involved in these more intensively researched diseases could result in more focussed results from the *in silico* analyses.

Following the identification of the likely targets of the multiple compounds contained in candidate herbs, future studies could extend the *in silico* analyses to virtually model the ligand – pharmacophore relationships of the identified compounds and targets.

References

1. Buxton PK, Morris-Jones R. ABC of dermatology. 5th ed. Oxford: Blackwell Publishing Ltd; 2009.

2. Weller R, Hunter J, Savin J, Dahl M. Clinical dermatology. 4th ed. Malden (USA)/ Oxford (UK)/ Carlton (Australia): USA, UK & Australia: Blackwell Publishing; 2009.

3. Langley RGB, Krueger GG, Griffiths CEM. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64(Suppl II):ii18-ii23.

4. Scottish Intercollegiate Guidelines Network. Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline 2010. Available from: http://www.sign.ac.uk/pdf/sign121.pdf (Accessed on 5 April 2011).

5. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol. 2008;58(6):1031-42.

6. Menter A, Griffiths C. Current and future management of psoriasis. Lancet. 2007;370(9583):272-84.

7. Graham-Brown R, Bourke J. Mosby's color atlas and text of dermatology. 2nd ed: Elsevier Limited.; 2007.

8. Bell LM, Sedlack R, Beard CM, Perry HO, Michet CJ, Kurlank LT. Incidence of psoriasis in Rochester, Minn, 1980-1983. Arch Dermatol. 1991;127:1184-7.

9. Neimann AL, Porter SB, Gelfand JM. The epidemiology of psoriasis. Expert Rev Dermatol. 2006;1(1):63-75.

10. Olsen AO, Grjibovski A, Magnus P, Tambs K, Harris JR. Psoriasis in Norway as observed in a population-based Norwegian twin panel. Br J Dermatol. 2005 153:346-51.

11. Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26:314-20.

12. Gelfand JM, Stern RS, Nijsten T, Feldman SR, Thomas J, Kist J, et al. The prevalence of psoriasis in African Americans: Results from a population-based study. J Am Acad Dermatol. 2005;52:23-6.

13. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom. Arch Dermatol. 2005;141:1537-41.

14. Cimmino MA. Epidemiology of psoriasis and psoriatic arthritis. Reumatismo. 2007;59 (Suppl 1):19-24.

15. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: Results from NHANES 2003-2004. J Am Acad Dermatol 2008;60:218-24.

16. Raychaudhuri S, Farber E. The prevalence of psoriasis in the world. J Eur Acad Dermatol Venereol. 2001;15:16–7.

17. Psoriasis Australia. Key statistics. Available from: http://home.vicnet.net.au/~psorias/ap_stats.shtml (Accessed on 11 March 2011).

18. Plunkett A, Merlin K, Gill D, Zuo Y, Jolley D, Marks R. The frequency of common nonmalignant skin conditions in adults in central Victoria, Australia. Int J Dermatol. 1999;38:901-8.

19. Ding X, Wang T, Shen Y, Wang X, Zhou C, Tian S, et al. Prevalence of psoriasis in China: An epidemiological survey in six provinces. Chin J Dermatol Venereol. 2010(07):598-601.

20. Li Y, Wang X, Ye Y, Liu F. Epidemiological survey of psoriasis in Xuzhou. Acta Acad Med Xuzhou. 1998;18(2):107 - 8.

21. National Survey Organization of Psoriasis Epidemiology. The survey report on the national psoriasis epidemiology in 1984. Dermatol Venereol. 1989(01):60-72.

22. Qian W. Epidemiological survey of psoriasis in Xinjiang. Acta Acad Med Xinjiang. 1978;2:204.

23. Xu Y, Tong Z, Shen S, Li C, He J, Yin J, et al. Epidemiological survey of rural residents with psoriasis in Suzhou, Anhui. Acta Universitatis Medicinalis Anhui. 2001;36(6):483- 5.

24. Zhang L, Sun B, Liu H, Huang F, Xu S, Liu F, et al. Epidemiological survey of Chinese Mongolian with psoriasis. Chin J Dermatol. 1989;25 (4):219- 21.

25. Radtke MA, Augustin M. Economic considerations in psoriasis management. Clin Dermatol. 2008;26 424-31.

26. Feldman SR, Garton R, Averett W, Balkrishnan R, Vallee J. Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost. Exper Opin Pharmacother. 2003;4(9):1525-33.

27. Javitz HS, Ward MM, Farber E, Nail L, Vallow SG. The direct cost of care for psoriasis and psoriatic arthritis in the United States. J Am Acad Dermatol. 2002;46(6):850-60.

28. Bureau of Labor Statistics. CPI Item Concordance - 1998 Revision 1998. Available from: http://www.bls.gov/cpi/cpiitemc.htm (Accessed on 06 November 2013).

29. Berger K, Ehlken B, Kugland B, Augustin M. Cost-of-illness in patients with moderate and severe chronic psoriasis vulgaris in Germany. J Dtsch Dermatol Ges. 2004;3:511-8.

30. Jenner N, Campbell J, Plunkett A, Marks R. Cost of psoriasis: A study on the morbidity and financial effects of having psoriasis in Australia. Aust J Dermatol. 2002;43:255-61.

31. Li Y, Dang Y, Yang X. The analysis of curative cost and long-term follow-up result of psoriasis. Chin Med Mod Dis Educ 2009;7(6):139-40.

32. Zhang WM, Wang AW, Ma JK, Li HM, Zhang ZB, Chen QZ, et al. China labour statistical yearbook 2004. Beijing: China Statistics Press; 2004.

33. Marchetti A, LaPensee K, An PM. A pharmacoeconomic analysis of topical therapies for patients with mild-to-moderate stable plaque psoriasis: A US study. Clin Ther. 1998;20(4):851-69.

34. Rashmi R, Rao KS, Basavaraj KH. A comprehensive review of biomarkers in psoriasis. Clin Exp Dermatol. 2009;34(6):658-63.

35. Traub M, Marshall K. Psoriasis - pathophysiology, conventional, and alternative approaches to treatment. Altern Med Rev. 2007;12(4):319-30.

36. Smith N, Weymann A, Tausk FA, Gelfand JM. Complementary and alternative medicine for psoriasis: a qualitative review of the clinical trial literature. J Am Acad Dermatol. 2009;61(5):841-56.

37. Li L. Treatment of psoriasis with traditional Chinese medicine. Hongkong: Hai Feng Publishing Co., Ltd.; 1990.

38. Buenz EH, Schnepple DJ, Bauer BA, Elkin PL, Riddle JM, Motley TJ. Techniques: Bioprospecting historical herbal texts by hunting for new leads in old tomes. Trends in Pharmacological Sciences. 2004;25(9):494-8.

39. Kong DX, Li XJ, Zhang HY. Where is the hope for drug discovery? Let history tell the future. Drug Discov Today. 2009;14(3-4):115-9.

40. Zhang H, Gu J. Progress of experimental study on treatment of psoriasis by Chinese medicinal monomer and single or compound recipe in Chinese materia medica. Chin J Integr Med. 2007;13(4):312-6.

41. Feily A, Namazi MR. Aloe vera in dermatology: a brief review. G Ital Dermatol Venereol. 2009;144(1):85-91.

42. Ulbricht C, Armstrong J, Basch E, S. B, Bent S, Dacey C, et al. An evidence-based systematic review of aloe vera by the natural standard research collaboration. J Herb Pharmacother. 2007;7(3-4):279-323.

43. Ulbricht C, Basch E, Barrette E-P, Bent S, Boon H, Hammerness PG, et al. Shark cartilage: An evidence-based systematic review for the natural standard research collaboration. J Cancer Integr Med. 2005;3(3):99-111.

44. Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. Br J Gen Pract. 1999;49(447):823-8.

45. Feng X, Xu L. Traditional Chinese medicine plus acitretin for psoriasis: a meta-analysis on randomized controlled trials. J Tianjin Med Univ. 2008;v.14;No.56(04):487-91.

46. Tang W, Zhou M, Lei Y. Evaluation of methodological quality on the randomized controlled trial of psoriasis with Chinese medicine. Liaoning J Trad Chin Med. 2006:2.

47. Levin C, Maibach H. Exploration of "alternative" and "natural" drugs in dermatology. Arch Dermatol. 2002;138(2):207-11.

48. Steele T, Rogers CJ, Jacob SE. Herbal remedies for psoriasis: what are our patients taking? Dermatol Nurs. 2007;19(5):448-50, 57-63.

49. Tse TW. Use of common Chinese herbs in the treatment of psoriasis. Clin Exp Dermatol. 2003;28(5):469-75.

50. Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. Arch Dermatol. 1998;134(11):1388-93.

51. Koo J, Desai R. Traditional Chinese medicine in dermatology. Dermatologic therapy. 2003;16(2):98-105.

52. Ouyang H. Progress in the treatment of psoriasis with TCM or Western Medicine. Guid J TCM. 2007;13(2):1-8.

53. Wu T, Jin X, Zhang M, Wei J. Traditional Chinese herbs for psoriasis (protocol). Cochrane Database of Systematic Reviews. 2009; (3). DOI:10.1002/14651858.CD005412.

54. Jensen P. Use of alternative medicine by patients with atopic dermatitis and psoriasis. Acta Derm Venereol. 1990;70(5):421-4.

55. Lin X-R. Psoriasis in China. J Dermatol. 1993;20:746-55.

56. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. J Am Acad Dermatol. 1993;29(3):428-34.

57. Gladman D, Anhorn K, Schachter R, Mervart H. HLA antigens in psoriatic arthritis. J Rheumatol. 1986;13(3):586-92.

58. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007;445:866-73.

59. Tagami H. Triggering factors. Clin Dermatol. 1997;15.

60. Eyre R, Krueger G. Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and 'reverse' Koebner reactions. Br J Dermatol 1982;106(2):153-9.

61. Johnson T, Duvic M, Rapini R, Rios A. AIDS exacerbates psoriasis. N Engl J Med. 1985;313(22):1415.

62. Colebunders R, Blot K, Mertens V, Dockx P. Psoriasis regression in terminal AIDS. The Lancet. 1992;339:1110.

63. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol. 2005;125(1):61-7.

64. Guenther LC, Ortonne JP. Pathophysiology of psoriasis: science behind therapy. J Cutan Med Surg. 2002;6(3 Suppl):2-7.

65. Lebwohl M. Psoriasis. Lancet. 2003;361:1197-204.

66. Jowitt SN, Liu JAY. Psoriasis and bone marrow transplantation. BMJ. 1990;300:1398-9.

67. Wahie S, Slexandoff A, Reynolds NJ, Meggitt SJ. Psoriasis occurring after myeloablative therapy and autologous stem cell transplantation. Br J Dermatol. 2006;154:177-204.

68. Chua RA, Arbiser JL. The role of angiogenesis in the pathogenesis of psoriasis. Autoimmunity. 2009;42(7):574-9.

69. MacDonald A, Burden AD. Psoriasis: advances in pathophysiology and management. Postgrad Med J. 2007;83(985):690-7.

70. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-71.

71. Myers WA, Gottlieb AB, Mease P. Psoriasis and psoriatic arthritis: clinical features and disease mechanisms. Clin Dermatol. 2006;24(5):438-47.

72. Drake LA, Ceilley RI, Cornelison RL, Dobes WA, Dorner W, Goltz RW, et al. Guidelines of care for psoriasis. J Am Acad Dermatol. 1993;28(4):632-7.

73. Weinstein GD, Menter MA. An Overview of Psoriasis. In: Weinstein GD, Gottlieb AB, editors. Therapy of moderate-to-severe psoriasis. 2nd ed, revised and expanded ed. New York: Marcel Dekker, Inc.; 2003. p. 1-28.

74. Rzany B, Naldi L, Schafer T, Stern R, Williams H. The diagnosis of psoriasis: diagnostic criteria. Br J Dermatol. 1998;138(5):917.

75. Menter A, Stoff B. Psoriasis. London: Manson Publishing Ltd; 2011.

76. Meier M, Sheth BP. Clinical spectrum and severity of psoriasis. In: Yawalkar N, editor. Management of Psoriasis. Basel: Karger; 2009. p. 1-20.

77. Ellis CN, Berberian B, Sulica VI, Dodd WA, Jarratt MT, Katz HI, et al. A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol. 1993;29(3):438-42.

78. Li ZX, Hui HY, Ji FP, Peng ZH. Triptolide ointment for 248 cases of hypertrophic plaque psoriasis. Chin J Dermatol. 2005;38(3):182-3.

79. Sun B. Chinese herb combined with cryotherapy for cutaneous amyloidosis. J Tradit Chin Med. 1988(11):56-7.

80. Mason A, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis (Review). The Cochrane Collaboration. 2009(2):1-565.

81. Zhao M, Guo J, Jia H. Light quantum oxygen transmission on compound Salvia miltiorrhiza fluid for psoriasis vulgaris. Ninxia Med J. 1999;21(5):310.

82. Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk J, Henry H. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad Dermatol. 1986;15(3):504-7.

83. Li S, Li S. Liandai Quexie Zhiyang capsule combined with ozone major autohaemotherapy for psoriasis vulgaris. Hebei J TCM. 2010;32(2):193.

84. Lu D. Combination therapy for psoriatic arthritis. J Snake. 2010;22(3):230-2.

85. Liu K, Luo ZC, Li WZ. Podophyllotoxin tincture for the localized plaque psoriasis. China J Lepr Skin Dis. 2005;21(8):621-2.

86. Gao WY, Zhang W, Yang YD, Zhou CY, Bei YC. Liubei Beige cream for psoriasis vulgaris. J Ext Ther TCM. 2006;15(2):26-7.

87. Durbertret L. Retinoids, Methotrexate and Cyclosporine. In: Yawalkar N, editor. Management of psoriasis. 38. Bern: Karger; 2009. p. 79-94.

88. Naldi L, Griffiths CEM. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. Br J Dermatol. 2005;152:597-615.

89. Wang JX, Zhu MF, Xiang LP, Xiao YL. Chinese medicinal bath for psoriasis vulgaris. J Chin Phys. 2002(01):96-7.

90. Wei Q. Chinese medicine principle "heat-purging to remove pathogen" for psoriasis. Chin J Conval Med. 1995;4(1):40, 2.

91. Wright RC. Chapter One: The history and philosophy of Chinese medicine. In: Gao D, editor. The encyclopedia of Chinese medicine: Carlton Books Limited; 1997.

92. Shan Z, Yang B. The origin and development of pharmaceutical preparation on Chinese medicinal herb. Shanxi J of TCM. 2005;21(04):55-6.

93. Han Z, Zhang W. Discussion on the evolvement of standardization on the ancient Chinese medicinal herb. Chinese Journal of Social Medicine. 1987(03):48-51+41.

94. Men J, Guo L. A general introduction to Traditional Chinese Medicine. Beijing; Boca Raton, London, New York: Science Press; CRC Press; 2010.

95. Lin Y. Chines original and development of formula study and pharmaceutical preparation on Chinese medicinal herb (I). Zhejiang Med J. 1984;6(3):63-5.

96. Shang Z. The earliest manufacturer of Chinese traditional patent drug in the Chinese history-'Compounding Bureau' in Song dynasty. Research Chinese Traditional Patent Medicine. 1981(7):43-5.

97. Wang A. The origin and development of pharmaceutical preparation on Chinese medicinal herbs. Chinese Pharmaceutical Journal. 1982;17(7):45-6.

98. Fan Y, Song P. Consideration of Traditional Chinese Medicine aetiology and pathology on psoriasis. Global Traditional Chinese Medicine. 20012;5(9):681-3.

99. Ma T, Liu L, Wang Y. The advance of Traditional Chinese Medicine etiology and pathology on psoriasis. Information on Traditional Chinese Medicine. 2005;22(4):23-4.

100. Feng X, Geng C, Wu M. Literature of Traditional Chinese Medicine aetiology and pathology on psoriasis. Modern Journal of Integrated Traditional Chinese and Western Medicine. 2009;18(8):932-3.

101. Maciocia G. The foundations of Chinese Medicine: a comprehensive text for acupuncturists and herbalists: Churchill Livingstone; 1989.

102. Wang H, Xu L. The Traditional Chinese Medicine physiology and pathology of psoriasis. Chinese Journal of Integrative Medicine on Dermatology and Venerology. 2009;8(1):56-8.

103. Zhou D. The clinical experience of bowel and visceral pattern identification for psoriasis. Chinese Journal of Emergency in Traditional Chinese Medicine. 2005;14(11):1080+5.

104. Jin L, Jiang Y, Ma Y, Lou W. Analysis of the relationship between the morbidity characteristics of psoriasis and the liver function in Traditional Chinese Medicine. Journal of Practical Dermatology. 2009;2(3):163-5.

105. Qin W. Blood syndrome of psoriasis and its blood management. Chinese Journal of Integrative Medicine on Dermatology and Venerology. 2008;7(1):1-4.

106. Xu F, Zhai Y, Min Z, Lu Z, editors. Surgery of Traditional Chinese Medicine. Shanghai, China: Publishing House of Shanghai University of Traditional Chinese Medicine; 2002.

107. Yu X, Xu W, Wu X, Wang T. Literature research on symptoms distribution of psoriasis vulgaris. Shanghai Zhong Yi Yao Da Xue Xue Bao. 2013;27(2):54-7.

108. Deng B. The discussion on TCM syndrome differentiation of psoriasis. Chinese Abstract of Medicine-Dermatology. 2007;24(6):344-5.

109. Li T, Xu X. Study on the Rule of distribution of TCM syndromes of psoriasis. JTCM. 2010;51(6):544-6.

110. Deng B, Jian C, Wang P, Liu W, Xu X, Zhao Y, et al. Rule of distribution and development of TCM syndromes of psoriasis. JTCM. 2006;47(10):770-2.

111. Zheng XY. The clinical research guidelines on Chinese medicinal herbs (Trial). Beijing, China: China Medical Science Press; 2002.

112. Zhang L, Zhou F. The existing circumstances of clinical research on the treatment based on syndrome differentiation of psoriasis. Chinese Journal of Integrative Medicine on Dermatology and Venereology. 2009;8(2):128-31.

113. Cha X, Chen X. Introduction of Prof. Xuan Guowei's clinical experiences for psoriasis. New J Tradit Chin Med. 2006;38(6):7-8.

114. Gu B. Selected clinical experiences of surgery. 1st ed. Shanghai, China: Shanghai People's Publishing House; 1977.

115. Jin Q. The Traditional Chinese Medicine management of psoriasis. Chinese Countryside Medicine. 1989(6):31-3.

116. Li L, Li B. Prestigious TCM practitioner Zhu Ren-kang's clinical experiences for psoriasis. JTCM. 1985;26(1):12-4.

117. Ma S, Li Y. The treatment of syndrome differentiation of 123 patients with psoriasis vulgaris. Hunan Herald of TCM. 1999;5(7):21.

118. Shi P. Zhao Bin-nan's clinical experiences for psoriasis. The 6th Annual Conference on Dermatology Branch, China Association of Chinese Medicine; Zhao Bing-nan Academic Thought Seminar; Beijing, China1999.

119. Wang L. Zhang Zhi-li's clinical experiences on psoriasis vulgaris with treatment based on syndrome differentiation. Shanxi J of TCM. 2007;23(5):10-1.

120. Xiang L. Ouyang Heng's clinical experiences for psoriasis. JTCM. 2008;49(1):13-4.

121. Li Y, Du Y. The evaluation of acupuncture for psoriasis in the recent 5 years. J Shanxi Coll of TCM. 2009;32(4):56-9.

122. Jerner B, Skogh M, Vahlquist A. A controlled trial of acupuncture in psoriasis: no convincing effect. Acta Derm Venereol. 1997;77(2):154-6.

123. Carlsson CP, Wallengren J. Therapeutic and experimental therapeutic studies on acupuncture and itch: review of the literature. J Eur Acad Dermatol Venereol. 2010;24(9):1013-6.

124. Napadow V, Li A, Loggia ML, Kim J, Schalock PC, Lerner E, et al. The brain circuitry mediating antipruritic effects of acupuncture. Cereb Cortex. 2014;24(4):873-82.

125. Liang J, Xia H, Liao F. Systematic mechanism of acupuncture in the management of psoriasis Sichuan J Tradit Chin Med. 2007;25(4):97-9.

126. Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Book Series. Chichester: John Wiley & Sons Ltd; 2008. p. 95-151.

127. Oral retinoids for psoriasis (Protocol). John Wiley & Sons, Ltd. 2009. Available from: www.thecochranelibrary.com.

128. Interventions for guttate psoriasis (Review). John Wiley & Sons, Ltd. 2009. Available from: www.thecochranelibrary.com.

129. Jiangsu New Medical Academy, editor. Zhong yao da ci dian 'Great Compendium of Chinese Medicines'. Shanghai: Shanghai Scientific and Technical Publishers; 1986.

130. Li JW, Yu YA, Cai JF, Zhang ZB, Ou YX, Deng TT, et al., editors. Zhong Yi Da Ci Dian 'Great Dictionary of Chinese Medicine'. 2 ed. Beijing: People's Medical Publishing House; 2005.

131. Menter A, Griffiths CEM. Current and future management of psoriasis. Lancet. 2007;370:272-84.

132. Moher D, Liberati A, Tetzlaff J, Altman D, Group TP. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med. 2009;6(7):1-7.

133. Higgins JP, Altman DG. Assessing risk of bias in included studies. In: Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions. Cochrane book series. Chichester: John Wiley & Sons Ltd; 2008. p. 187-242.

134. Shi J, Tong Y, Shen J, Li H. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: A systematic review. World J Gastroenterol. 2008;14(3):454-62.

135. Deng S, May BH, Zhang AL, Lu C, Xue CC. Phytotherapy in the management of psoriasis: a review of the efficacy and safety of oral interventions and the pharmacological actions of the main plants. Arch. Dermatol. Res. DOI 10.1007/s00403-013-1428-4. 2013 Nov 20.

136. Gulliver WP, Donsky HJ. A report on three recent clinical trials using Mahonia aquifolium 10% topical cream and a review of the worldwide clinical experience with Mahonia aquifolium for the treatment of plaque psoriasis. Am J Ther 2005;12(5):398-406.

137. Benhard JD, Kristeller J, Kabat-Zinn J. Effectiveness of relaxation and visualization techniques as an adjunct to phototherapy and photochemotherapy of psoriasis. J Am Acad Dermatol. 1988;19(3):572-4.

138. Gaston L, Crombez JC, Lassonde M, Bernier-Buzzanga J, Hodgins S. Psychological stress and psoriasis: experimental and prospective correlational studies. Acta Derm Venereol Suppl (Stockh). 1991;156:37-43.

139. Kabat-Zinn J, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, et al. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). Psychosom Med. 1998;60(5):625-32.

140. Lazaroff I, Shimshoni R. Effects of Medical Resonance Therapy Music on patients with psoriasis and neurodermatitis--a pilot study. Integr Physiol Behav Sci. 2000;35(3):189-98.

141. Leibovici V, Magora F, Cohen S, Ingber A. Effects of virtual reality immersion and audiovisual distraction techniques for patients with pruritus. Pain Res Manag. 2009;14(4):283-6.

142. Price ML, Mottahedin I, Mayo PR. Can psychotherapy help patients with psoriasis? Clin Exp Dermatol. 1991;16(2):114-7.

143. Relman A, Riley D, Kabat-Zinn J, Hosmer D. Parsing the data: An examination of a study on meditation and the treatment of psoriasis. Adv Mind Body Med. 2001;17(1):66-7.

144. Tang H, Dai D, Tao L. Xiaoyao Wan combined Traditional Chinese Medicine psychological intervention for psoriasis. J Liaoning Univ TCM. 2006(06):114-5.

145. Tausk F, Whitmore SE. A pilot study of hypnosis in the treatment of patients with psoriasis. Psychother Psychosom. 1999;68(4):221-5.

146. Zachariae R, Oster H, Bjerring P, Kragballe K. Effects of psychologic intervention on psoriasis: a preliminary report. J Am Acad Dermatol. 1996;34(6):1008-15.

147. Zhang J, Deng Y, Ye T, Yang C, Hu X, Yang W. Psychological intervention combined with Xiaobi Tang for 42 patients with psoriasis vulgaris. New J Tradit Chin Med. 2011;43(11):61-2.

148. Madland TM, Bjorkkjaer T, Brunborg LA, Froyland L, Berstad A, Brun JG. Subjective improvement in patients with psoriatic arthritis after short-term oral treatment with seal oil. A pilot study with double blind comparison to soy oil. J Rheumatol. 2006;33(2):307-10.

149. Gupta AK, Ellis CN, Goldfarb MT, Hamilton TA, Voorhees JJ. The role of fish oil in psoriasis: A randomized, double-blind, placebo-controlled study to evaluate the effect of fish oil and topical corticosteroid therapy in psoriasis. Int J Dermatol. 1990;29(8):591-5.

150. Drouin R, Moroni O, Cantin K, Juneau C. A double-blind, placebo-controlled, randomized trial of XP-828L (800 mg) on the quality of life and clinical symptoms of patients with mild-to-moderate psoriasis. Altern Med Rev. 2008;13(2):145-52.

151. Poulin Y, Bissonnette R, Juneau C, Cantin K, Drouin R, Poubelle PE. XP-828L in the treatment of mild-to-moderate psoriasis: A randomized, double-blind, placebo-controlled study. Altern Med Rev. 2007;12(4):352-9.

152. Shani J, Kushelevsky AP, Harari M, Even-Paz Z. Sustained decrease of blood pressure in psoriatic patients during treatment at the Dead Sea. Pharmacol Res. 1995;31(6):355-9.

153. Liu H, Gao X, Li G, Cao R, Zhou C, Wang X, et al. Salvia miltiorrhiza intravenous infusion combined with UV plus Ultraviolet Blood Irradiation and Oxygenation (UBIO) for psoriasis. Tianjin Med J. 2000;28(1):54-5.

154. Liu X, Xusheng W. Chinese herbs combination with laser hemotherapeutics for psoriasis vulgaris. Chin J Infor Trad Chin Med. 2001;8(1):73.

155. Wang J, Liu J. 70 nursing cases of psoriasis with intravascular low lever He-Ne laser irradiation on blood. J Qilu Nurs. 2005;11(19):1842.

156. El Zawahry M. The Egyptian sycamore tree: its use in dermatology. Int J Dermatol. 1977;16(10):853-4.

157. Deng S, May BH, Zhang AL, Lu C, Xue CC. Topical herbal medicine combined with pharmacotherapy for psoriasis: a systematic review and meta-analysis. Arch. Dermatol. Res. 2013;305(3):179-89.

158. Deng S, May BH, Zhang AL, Lu C, Xue CC. Topical herbal formulae in the management of psoriasis: systematic review with meta-analysis of clinical studies and investigation of the pharmacological actions of the main herbs. Phytother Res. doi:10.1002/ptr.5028. 1 July 2013.

159. Deng S, May BH, Zhang AL, Lu C, Xue CC. Plant extracts for the topical management of psoriasis: a systematic review and meta-analysis. The British journal of dermatology. 2013;169(4):769-82.

160. Baron SE, Goodwin RG, Nicolau N, Blackford S, Goulden V. Use of complementary medicine among outpatients with dermatologic conditions within Yorkshire and South Wales, United Kingdom. J Am Acad Dermatol. 2005;52(4):589-94.

161. Fuhrmann T, Smith N, Tausk F. Use of complementary and alternative medicine among adults with skin disease: updated results from a national survey. J Am Acad Dermatol. 2010;63(6):1000-5.

162. Smith N, Shin DB, Brauer JA, Mao J, Gelfand JM. Use of complementary and alternative medicine among adults with skin disease: results from a national survey. J Am Acad Dermatol. 2009;60(3):419-25.

163. Feng X, Xu L. Traditional Chinese medicine plus acitretin for psoriasis: A meta-analysis on randomized controlled trials. J Tianjin Med Univ. 2008;14(4):487-91.

164. Li N, Li YQ, Li HY, Guo W, Bai YP. Efficacy of externally applied Chinese herbal drugs in treating psoriasis: a systematic review. Chin J Integr Med. 2012;18(3):222-9.

165. May BH, Zhang AL, Zhou W, Lu CJ, Deng S, Xue CC. Oral herbal medicines for psoriasis: A review of clinical studies. Chin J Integr Med. 2012;18(3):172-8.

166. Reuter J, Wölfle U, Weckesser S, Schempp C. Which plant for which skin disease? Part 1: Atopic dermatitis, psoriasis, acne, condyloma and herpes simplex. JDDG. 2010;8:788–96.

167. Sucher NJ. The application of Chinese medicine to novel drug discovery. Expert opinion on drug discovery. 2012.

168. Lee M, Kalb RE. Systemic therapy for psoriasis. Dermatol Nurs. 2008;20(2):105-11.

169. Naldi L, Griffiths CEM. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. Br J Dermatol. 2005;152:597-615.

170. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. J Am Acad Dermatol. 2012;66(3):369-75.

171. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies Chichester, UK: John Wiley & Sons Ltd; 2012. p187-242. Available from: www. cochrane-handbook.org (Accessed on 10 October 2012).

172. Sterne JA, Egger M, Moher D. Chapter 10: Addressing reporting biases Chichester, UK John Wiley & Sons Ltd 2012. p 297-333. Available from: www. cochrane-handbook.org (Accessed on 12 October 2012).

173. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004;50(6):859-66.

174. Fan M, Song X, Wang W, Cai Y, Sun L, Jiang L. Lanchuan Qingre decoction for psoriasis. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2005;25(4):375-6.

175. Ho SG, Yeung CK, Chan HH. Methotrexate versus traditional Chinese medicine in psoriasis: A randomized, placebo-controlled trial to determine efficacy, safety and quality of life. Clin Exp Dermatol. 2009. DOI: 10.1111/j.1365-2230.2009.03693.x.

176. Ma W, Qu Y, Pan H, Jiang S. Efficacy of 52 cases on psoriasis formula for blood-heat type psoriasis vulgaris. New J Tradit Chin Med. 2010;42(11):68-70.

177. Pandey SS, Jha AK, Kaur V. Aqueous extract of neem leaves in treatment of psoriasis vulgaris. Indian J Dermatol Venereol Leprol. 1994;60(2):63-7.

178. Qiu S, Tan S, Sun Z, Zhang J, Yuan J, Liu P. Huoxue Sanyu Xiaoyin Tang for psoriasis vulgaris. Zhong Yao Cai. 2005;28(5):442-4.

179. Wu Y, Zhou Q, Xu Q, Shui R, Fan W, He F, et al. Qinre Jiedu Tang for blood-heat type elderly psoriasis. Geriatr & Health Care. 2003;9(4):240-2.

180. Xie S, Yi X, Yang L, Li Y. Clinical observation of 41 cases of psoriasis vulgaris with 1 Kang Yin Fang. Hebei J Tradit Chin Med. 2009;31(2):173-5.

181. Zhang F, Tian R, Ma S, Wang X, Yu M, Shi Z. Treatment of active psoriasis vulgaris with Tripterygium wilfordii -- double blind controlled trial. Journal of Clinical Dermatology. 1999;28(1):32-3.

182. Zhang H, Sun J, Liu T, Liu X, Feng L, Sun H. Compound Zeqi granule for the progressive psoriasis vulgaris and its effect on serum TNF-α and IL-8. Chin J Derm Venereol. 2008;128(5):281-2.

183. Zhang M, Zhang YZ, Wang S. The effect of acitretin on moderate to severe plaque psoriasis. J Clin Dermatol. 2007;36(9):592-3.

184. Zhang A, Qu Y, Zhang B, Zhang L, Zeng C, Peng J, et al. The different effects of indirubin on effector and CD4+CD25+ regulatory T cells in mice: potential implication for the treatment of autoimmune diseases. J Mol Med (Berl). 2007;85(11):1263-70.

185. Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. Chichester, UK: John Wiley & Sons Ltd; 2012. p 335-57. Available from: www. cochrane-handbook.org (Accessed on 12 October 2012).

186. Ho SG, Yeung CK, Chan HH. Methotrexate versus traditional Chinese medicine in psoriasis: A randomized, placebo-controlled trial to determine efficacy, safety and quality of life. Clin Exp Dermatol DOI:10.1111/j.1365-2230.2009.03693.x. 2009.

187. Jang J, Seo E, Han C, Chae H, Kim S, Lee J, et al. Four cases of toxic liver injury associated with Dictamnus dasycarpus. Korean J Hepatol. 2008;14(2):206-12.

188. Kane J, Kane S, Jain S. Hepatitis induced by traditional Chinese herbs; possible toxic components. Gut. 1995;36:146-7.

189. McRae C, Agarwal K, Mutimer D, Bassendine M. Hepatitis associated with Chinese herbs. Eur J Gastroenterol Hepatol. 2002;14(5):559-62.

190. Paik SW, Rhee JC, Kim JJ, Koh KC, Lee HY, Rhee PL, et al. Drug induced liver disease caused by ingestion of Dictamnus dasycarpus. Korean J Gastroenterol. 1998;31:251-7.

191. Canter PH, Lee HS, Ernst E. A systematic review of randomised clinical trials of Tripterygium wilfordii for rheumatoid arthritis. Phytomedicine. 2006;13(5):371-7.

192. Wang Q, Hu M. Pharmacological effects and side effects of triptolide. China Pharmaceuticals. 2010;19(19):85-6.

193. Kaur G, Sarwar Alam M, Athar M. Nimbidin suppresses functions of macrophages and neutrophils: relevance to its antiinflammatory mechanisms. Phytother Res. 2004;18(5):419-24.

194. Priyadarsini RV, Manikandan P, Kumar GH, Nagini S. The neem limonoids azadirachtin and nimbolide inhibit hamster cheek pouch carcinogenesis by modulating xenobiotic-metabolizing enzymes, DNA damage, antioxidants, invasion and angiogenesis. Free Radic. Res. 2009;43(5):492-504.

195. Manikandan P, Letchoumy PV, Gopalakrishnan M, Nagini S. Evaluation of Azadirachta indica leaf fractions for in vitro antioxidant potential and in vivo modulation of biomarkers of chemoprevention in the hamster buccal pouch carcinogenesis model. Food Chem Toxicol. 2008;46(7):2332-43.

196. Paul R, Prasad M, Sah NK. Anticancer biology of Azadirachta indica L (neem): a mini review. Cancer biology & therapy. 2011;12(6):467-76.

197. Subapriya R, Bhuvaneswari V, Ramesh V, Nagini S. Ethanolic leaf extract of neem (Azadirachta indica) inhibits buccal pouch carcinogenesis in hamsters. Cell biochemistry and function. 2005;23(4):229-38.

198. Brahmachari G. Neem--an omnipotent plant: a retrospection. Chembiochem: a European journal of chemical biology. 2004;5(4):408-21.

199. Reutemann P, Ehrlich A. Neem oil: an herbal therapy for alopecia causes dermatitis. Dermatitis : contact, atopic, occupational, drug : official journal of the American Contact Dermatitis Society, North American Contact Dermatitis Group. 2008;19(3):E12-5.

200. Khan PK, Awasthy KS. Cytogenetic toxicity of neem. Food Chem Toxicol. 2003;41(10):1325-8.

201. Srivastava MK, Raizada RB. Lack of toxic effect of technical azadirachtin during postnatal development of rats. Food Chem Toxicol. 2007;45(3):465-71.

202. Owolabi LL, Gbotolorun SC, Akpantah AO, Ekong MO, Eluwa MA, Ekanem TB. Effect of methanolic extract of Neem leaf (Azadirachta indica) on ovarian histology and hormonal milleu. Nig Q J Hosp Med. 2008;18(4):194-7.

203. Deng YX, Cao M, Shi DX, Yin ZQ, Jia RY, Xu J, et al. Toxicological evaluation of neem (Azadirachta indica) oil: acute and subacute toxicity. Environ. Toxicol. Pharmacol. 2013;35(2):240-6.

204. Ashafa AO, Orekoya LO, Yakubu MT. Toxicity profile of ethanolic extract of Azadirachta indica stem bark in male Wistar rats. Asian Pac J Trop Biomed. 2012;2(10):811-7.

205. Boeke SJ, Boersma MG, Alink GM, van Loon JJ, van Huis A, Dicke M, et al. Safety evaluation of neem (Azadirachta indica) derived pesticides. J Ethnopharmacol. 2004;94(1):25-41.

206. Mbah AU, Udeinya IJ, Shu EN, Chijioke CP, Nubila T, Udeinya F, et al. Fractionated neem leaf extract is safe and increases CD4+ cell levels in HIV/AIDS patients. Am J Ther. 2007;14(4):369-74.

207. Lamel SA, Myer KA, Younes N, Zhou JA, Maibach H, Maibach HI. Placebo response in relation to clinical trial design: a systematic review and meta-analysis of randomized controlled trials for determining biologic efficacy in psoriasis treatment. Arch. Dermatol. Res. 2012;304(9):707-17.

208. Wagner H. Synergy research: approaching a new generation of phytopharmaceuticals. Fitoterapia. 2011;82(1):34-7.

209. Augustin M, Andrees U, Grimme H, Schopf E, Simon J. Effects of Mahonia aquifolium ointment on the expression of adhesion, proliferation, and activation markers in the skin of patients with psoriasis. Forsch Komplementarmed. 1999;6 (Suppl 2):19-21.

210. Bernstein S, Donsky H, Gulliver W, Hamilton D, Nobel S, Norman R. Treatment of mild to moderate psoriasis with Relieva, a Mahonia aquifolium extract--a double-blind, placebo-controlled study. Am J Ther. 2006;13(2):121-6.

211. Brown AC, Koett J, Johnson DW, Semaskvich NM, Holck P, Lally D, et al. Effectiveness of kukui nut oil as a topical treatment for psoriasis. Int J Dermatol. 2005;44(8):684-7.

212. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. A prospective, randomized clinical trial comparing topical Aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. J Eur Acad Dermatol Venereol. 2010;24(2):168-72.

213. Gulliver WP, Donsky HJ. A report on three recent clinical trials using Mahonia aquifolium 10% topical cream and a review of the worldwide clinical experience with Mahonia aquifolium for the treatment of plaque psoriasis. Am J Ther. 2005;12(5):398-406.

214. Lin YK, Chang CJ, Chang YC, Wong WR, Chang SC, Pang JH. Clinical assessment of patients with recalcitrant psoriasis in a randomized, observer-blind, vehicle-controlled trial using indigo naturalis. Arch Dermatol. 2008;144(11):1457-64.

215. Lin YK, Wong WR, Chang YC, Chang CJ, Tsay PK, Chang SC, et al. The efficacy and safety of topically applied Indigo naturalis ointment in patients with plaque-type psoriasis. Dermatology. 2007;214(2):155-61.

216. Paulsen E, Korsholm L, Brandrup F. A double-blind, placebo-controlled study of a commercial Aloe vera gel in the treatment of slight to moderate psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2005;19(3):326-31.

217. Syed TA, Ahmad SA, Holt AH, Ahmad SH, Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study. Trop Med Int Health. 1996;1(4):505-9.

218. Wang A, Liu Z, Liu S, Hu J, Lei G. Treatment of psoriasis vulgaris with lacquer made of Camptotheca acuminata nuts J Clin Dermatol. 1998;27(4):243-4.

219. Wiesenauer M, Ludtke R. Mahonia aquifolim in patients with psoriasis vulgaris-an intraindividual study. Phytomedicine. 1996;3(3):231-5.

220. Lin YK, See LC, Huang YH, Chang YC, Tsou TC, Leu YL, et al. Comparison of refined and crude Indigo naturalis ointment in treating psoriasis: randomized, observer-blind, controlled, intrapatient trial. Arch Dermatol. 2012;148(3):397-400.

221. Lin YK, Wong WR, Su Pang JH. Successful treatment of recalcitrant psoriasis with Indigo naturalis ointment. Clin Exp Dermatol. 2007;32:95-116.

222. Lin YK, Yen HR, Wong WR, Yang SH, Su Pang JH. Successful treatment of pediatric psoriasis with Indigo naturalis composite ointment. Pediatr Dermatol. 2006;23(5):507–10.

223. Lin YK, See LC, Chang YC, Huang YH, Chen JL, Tsou TC, et al. Treatment of psoriatic nails with Indigo naturalis oil extract: a non-controlled pilot study. Dermatology. 2011;223(3):239-43.

224. Bensky D, Barolet R. Chinese herbal medicine: Formulas & strategies. 1st ed. Seattle, Washington: Eastland Press, Incorporated; 1990.

225. Gao WY, Zhang W, Yang YD, Zhou CY, Bei YC. Liubei Beibi cream for psoriasis vulgaris. J Ext Ther TCM. 2006;15(2):26-7.

226. Lassus A, Forsström S. A double-blind study comparing oleum horwathiensis with placebo in the treatment of psoriasis. J Int Med Res. 1991;19(2):137-46.

227. Lu YP, Miao XR. The topical application of Queyin tincture on psoriasis. Liaoning J Trad Chin Med. 2004(05):394.

228. Song P, Yan ZF, Xu X. Clinical observation on effect of compound E-bei ointment in treating plaque psoriasis. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2007;27(4):352-4.

229. Wang JX, Zhu MF, Xiang LP, Xiao YL. Chinese medicinal bath for psoriasis vulgaris. J Chin Phys. 2002(01):96-7.

230. Xu J, Zhang C, Qu X. Clinical and experimental study on effect of Qinbai ointment in treating psoriasis in the active stage of blood-heat syndrome type. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2009;29(7):614-8.

231. Yang YD, Zhang W, Gao WY, Yang WT, Zhang YL, Zhang L. Liubai Baibi cataplasm for psoriasis. J China Tradit Chin Med Inf. 2011;3(17):148.

232. Zhou N, Bai YP, Man XH, Zhang YB, Kong YH, Ju H, et al. Effect of New Pulian Ointment in treating psoriasis of blood-heat syndrome: A randomized controlled trial. Chin J Integr Med. 2009;15(6):409-14.

233. Zhu L, Zhang H, Duan Y. Chinese herbal medicine "Xiaoxuanling" for 85 participants with psoriasis vulgaris. Youjiang Med J. 2008;36(2):230-1.

234. Zhou H, Lutterodt H, Cheng Z, Yu LL. Anti-inflammatory and antiproliferative activities of trifolirhizin, a flavonoid from Sophora flavescens roots. J Agric Food Chem. 2009;57:4580–5.

235. Sun Y, Qin Y, Gong F-Y, Wu X-F, Hua Z-C, Chen T, et al. Selective triggering of apoptosis of concanavalin A-activated T cells by fraxinellone for the treatment of T-cell-dependent hepatitis in mice. Biochem Pharmacol. 2009;77:1717–24.

236. Garduno J, Bhosle MJ, Balkrishnan R, Feldman SR. Measures used in specifying psoriasis lesion(s), global disease and quality of life: A systematic review. J Dermatolog Treat. 2007;18(4):223-42.

237. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: A European consensus. Arch. Dermatol. Res.. 2011;303(1):1-10.

238. Feng Y, Zhao Q, Li Y, Cai R, Bai X. Efficacy of Chinese herbal bath in the treatment of psoriasis vulgaris. China J Lepr Skin Dis. 2007;23(01):88-9.

239. Han C, Peng J, Ye X. The clinical observation of the combination of Binghuangfule ointment and clobetasol cream for treating psoriasis vulgaris. Chin J Derm Venereol. 2006;20(2).

240. Liu XJ, Shi N, Chen YJ. Binghuang ointment for stable psoriasis vulgaris. Hubei J Tradit Chin Med. 2012;34(06):46.

241. Tang Y. Medicated bath for psoriasis vulgaris. Chin Nurs Res. 2004;18:1180.

242. Wang H, Sun Y, Li X. Efficacy of Chinese Medicine integrated with Western Medicine in 42 cases of psoriasis vulgaris. China Mod Dr. 2010(30):55+67.

243. Wang M, Sui S, Gong A, Guan Y, Kuang X. Efficacy of Yinxieling ointment on 675 cases. Chin Tradit Pat Med. 1990;12(11):21.

244. Yang H, Wu Y, Ding Y. Thymosin combined with Chinese herbal bath for psoriasis vulgaris in 82 cases. Shandong Med J. 2008;48(6):75.

245. Yang X, Du Y, Hu P, Chen D. Acitretin combined with Chinese herbal steam for psoriasis vulgaris. Chin J Dermatol Venereol. 2008;22(5):285-6.

246. Lin YK, Leu YL, Yang SH, Chen HW, Wang CT, Pang JH. Anti-psoriatic effects of Indigo naturalis on the proliferation and differentiation of keratinocytes with indirubin as the active component. J Dermatol Sci. 2009;54(3):168-74.

247. Dong P, Tu S. Procaine intravenous closure treatment for 84 proliferative and itching skin disorders. Chinese Journal for Clinicians. 2001;29(5):37-8.

248. Zhou J, Zhang D, He Y. Procaine intravenous closure treatment for generalized neurodermatitis. Medical Journal of National Defending Forces in Southwest China. 2002;12(3):254.

249. Li J, Li B, Wang G, Wang Q. The clinical application of procaine. Herald of Medicine. 2003;25(9):699-700.

250. Ye A. Development of the clinical application of ammonium glycyrrhizinate. Her Med. 1999;18(4):275-6.

251. Bhatia SP, McGinty D, Letizia CS, Api AM. Fragrance material review on l-borneol. Food Chem Toxicol. 2008;46 (Suppl 11):S81-4.

252. Tan L, Deng J. Development of chemical compounds and pharmacological activated constituents on Oldenlandia diffusa. Nei Mongol J Tradit Chin Med. 2008;27(4):42-5.

253. Gu G, Barone I, Gelsomino L, Giordano C, Bonofiglio D, Statti G, et al. Oldenlandia diffusa extracts exert antiproliferative and apoptotic effects on human breast cancer cells through ERalpha/Sp1-mediated p53 activation. J Cell Physiol. 2012;227(10):3363-72.

254. Song YH, Jeong SJ, Kwon HY, Kim B, Kim SH, Yoo DY. Ursolic acid from Oldenlandia diffusa induces apoptosis via activation of caspases and phosphorylation of glycogen synthase kinase 3 beta in SK-OV-3 ovarian cancer cells. Biol Pharm Bull. 2012;35(7):1022-8.

255. Yang L, Liu X, Lu Z, Yuet-Wa Chan J, Zhou L, Fung KP, et al. Ursolic acid induces doxorubicin-resistant HepG2 cell death via the release of apoptosis-inducing factor. Cancer Lett. 2010;298(1):128-38.

256. Harmand PO, Duval R, Delage C, Simon A. Ursolic acid induces apoptosis through mitochondrial intrinsic pathway and caspase-3 activation in M4Beu melanoma cells. International journal of cancer Journal international du cancer. 2005;114(1):1-11.

257. Kowalczyk MC, Walaszek Z, Kowalczyk P, Kinjo T, Hanausek M, Slaga TJ. Differential effects of several phytochemicals and their derivatives on murine keratinocytes in vitro and in vivo: Implications for skin cancer prevention. Carcinogenesis. 2009;30(6):1008-15.

258. Wojciak-Kosior M, Paduch R, Matysik-Wozniak A, Niedziela P, Donica H. The effect of ursolic and oleanolic acids on human skin fibroblast cells. Folia histochemica et cytobiologica / Polish Academy of Sciences, Polish Histochemical and Cytochemical Society. 2011;49(4):664-9.

259. Kim SJ, Chung WS, Kim SS, Ko SG, Um JY. Antiinflammatory effect of Oldenlandia diffusa and its constituent, hentriacontane, through suppression of caspase-1 activation in mouse peritoneal macrophages. Phytother Res. 2011;25(10):1537-46.

260. Kim SJ, Kim YG, Kim DS, Jeon YD, Kim MC, Kim HL, et al. Oldenlandia diffusa mmeliorates dextran sulphate sodium-induced Colitis through inhibition of NF-kappaB activation. Am J Chin Med. 2011;39(5):957-69.

261. Kang SY, Yoon SY, Roh DH, Jeon MJ, Seo HS, Uh DK, et al. The anti-arthritic effect of ursolic acid on zymosan-induced acute inflammation and adjuvant-induced chronic arthritis models. The Journal of pharmacy and pharmacology. 2008;60(10):1347-54.

262. Choi JK, Oh HM, Lee S, Park JW, Khang D, Lee SW, et al. Oleanolic acid acetate inhibits atopic dermatitis and allergic contact dermatitis in a murine model. Toxicol Appl Pharmacol. 2013.

263. Lim SW, Hong SP, Jeong SW, Kim B, Bak H, Ryoo HC, et al. Simultaneous effect of ursolic acid and oleanolic acid on epidermal permeability barrier function and epidermal keratinocyte differentiation via peroxisome proliferator-activated receptor-alpha. J Dermatol. 2007;34(9):625-34.

264. Lee HK, Nam GW, Kim SH, Lee SH. Phytocomponents of triterpenoids, oleanolic acid and ursolic acid, regulated differently the processing of epidermal keratinocytes via PPAR-alpha pathway. Exp Dermatol. 2006;15(1):66-73.

265. Pollier J, Goossens A. Oleanolic acid. Phytochemistry. 2012;77:10-5.

266. Sultana N. Clinically useful anticancer, antitumor, and antiwrinkle agent, ursolic acid and related derivatives as medicinally important natural product. J Enzyme Inhib Med Chem. 2011;26(5):616-42.

267. Sultana N, Ata A. Oleanolic acid and related derivatives as medicinally important compounds. J Enzyme Inhib Med Chem. 2008;23(6):739-56.

268. Choi JK, Oh HM, Lee S, Park JW, Khang D, Lee SW, et al. Oleanolic acid acetate inhibits atopic dermatitis and allergic contact dermatitis in a murine model. Toxicol Appl Pharmacol. 2013 Mar 13. Available from: http://dx.doi.org/10.1016/j.taap.2013.03.001.

269. Zeng Y, Jia ZP, Zhang RX. The chemical constituent Rehmannia glutinosa and its pharmacological research advance. Chinese Traditional Patent Medicine. 2006;28(04):609-11.

270. Kim H, Lee E, Lee S, Shin T, Kim Y, Kim J. Effect of Rehmannia glutinosa on immediate type allergic reaction. Int J Immunopharmacol. 1998;20(4-5):231-40.

271. Baek GH, Jang YS, Jeong SI, Cha J, Joo M, Shin SW, et al. Rehmannia glutinosa suppresses inflammatory responses elicited by advanced glycation end products. Inflammation. 2012;35(4):1232-41.

272. Liu CL, Cheng L, Ko CH, Wong CW, Cheng WH, Cheung DW, et al. Bioassay-guided isolation of anti-inflammatory components from the root of Rehmannia glutinosa and its underlying mechanism via inhibition of iNOS pathway. J Ethnopharmacol. 2012;143(3):867-75.

273. Wei XL, Ru XB. Effects of low-molecular-weight Rehmannia glutinosa polysaccharides on p53 gene expression. Zhongguo yao li xue bao = Acta pharmacologica Sinica. 1997;18(5):471-4.

274. Pungitore CR, Ayub MJ, Garcia M, Borkowski EJ, Sosa ME, Ciuffo G, et al. Iridoids as allelochemicals and DNA polymerase inhibitors. J Nat Prod. 2004;67(3):357-61.

275. Garcia C, Leon LG, Pungitore CR, Rios-Luci C, Daranas AH, Montero JC, et al. Enhancement of antiproliferative activity by molecular simplification of catalpol. Bioorg Med Chem. 2010;18(7):2515-23.

276. Pungitore CR, Leon LG, Garcia C, Martin VS, Tonn CE, Padron JM. Novel antiproliferative analogs of the Taq DNA polymerase inhibitor catalpol. Bioorg Med Chem Lett. 2007;17(5):1332-5.

277. Li CG, Sheng SJ, Pang EC, May B, Xue CC. HPLC profiles and biomarker contents of Australian-grown Salvia miltiorrhiza f. alba roots. Chem Biodivers. 2009;6(7):1077-86.

278. Wang X, Morris-Natschke SL, Lee KH. New developments in the chemistry and biology of the bioactive constituents of Tanshen. Med Res Rev. 2007;27(1):133-48.

279. Wu H. Research on pharmacological function of Salvia miltiorrhiza. Acta Acad Zhejiang Univ Tradit Chin Med. 2008;32(5):694-5.

280. Zhang Y, Jiang P, Ye M, Kim SH, Jiang C, Lu J. Tanshinones: sources, pharmacokinetics and anti-cancer activities. Int J Mol Med Sci. 2012;13(10):13621-66.

281. Zhou L, Zuo Z, Chow MS. Danshen: An overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. J Clin Pharmacol. 2005;45(12):1345-59.

282. Parajuli DR, Park EJ, Che XH, Jiang WY, Kim YC, Sohn DH, et al. PF2401-SF, standardized fraction of Salvia miltiorrhiza, induces apoptosis of activated hepatic stellate cells in vitro and in vivo. Molecules. 2013;18(2):2122-34.

283. Li FL, Xu R, Zeng QC, Li X, Chen J, Wang YF, et al. Tanshinone IIA inhibits growth of keratinocytes through cell cycle arrest and apoptosis: Underlying treatment mechanism of psoriasis. Evid Based Complement Alternat Med. 2012;2012:927658.

284. Ma H, Fan Q, Yu J, Xin J, Zhang C. Novel microemulsion of tanshinone IIA, isolated from Salvia miltiorrhiza Bunge, exerts anticancer activity through inducing apoptosis in hepatoma cells. Am J Chin Med. 2013;41(1):197-210.

285. Liu L, Jia J, Zeng G, Zhao Y, Qi X, He C, et al. Studies on immunoregulatory and anti-tumor activities of a polysaccharide from Salvia miltiorrhiza Bunge. Carbohydr Polym. 2013;92(1):479-83.

286. Li M, Zhang L, Cai RL, Gao Y, Qi Y. Lipid-soluble extracts from Salvia miltiorrhiza inhibit production of LPS-induced inflammatory mediators via NF-kappaB modulation in RAW 264.7 cells and perform antiinflammatory effects in vivo. Phytother Res. 2012;26(8):1195-204.

287. Jang SI, Kim HJ, Kim YJ, Jeong SI, You YO. Tanshinone IIA inhibits LPS-induced NF-kappaB activation in RAW 264.7 cells: possible involvement of the NIK-IKK, ERK1/2, p38 and JNK pathways. Eur J Pharmacol. 2006;542(1-3):1-7.

288. Li FL, Xu R, Zeng QC, Li X, Chen J, Wang YF, et al. Tanshinone IIA inhibits growth of keratinocytes through cell cycle arrest and apoptosis: Underlying treatment mechanism of psoriasis. eCAM. 2012. DOI: 10.1155/2012/927658.

289. Rishi P, Rampuria A, Tewari R, Koul A. Phytomodulatory potentials of Aloe vera against Salmonella OmpR-mediated inflammation. Phytother Res. 2008;22(8):1075-82.

290. Tarameshloo M, Norouzian M, Zarein-Dolab S, Dadpay M, Gazor R. A comparative study of the effects of topical application of Aloe vera, thyroid hormone and silver sulfadiazine on skin wounds in Wistar rats. Lab Anim Res. 2012;28(1):17-21.

291. Panahi Y, Davoudi SM, Sahebkar A, Beiraghdar F, Dadjo Y, Feizi I, et al. Efficacy of Aloe vera/olive oil cream versus betamethasone cream for chronic skin lesions following sulfur mustard exposure: a randomized double-blind clinical trial. Cutan Ocul Toxicol. 2012;31(2):95-103.

292. Dat AD, Poon F, Pham KB, Doust J. Aloe vera for treating acute and chronic wounds. Cochrane Database Syst Rev. 2012(2):CD008762.

293. Dhanabal SP, Priyanka Dwarampudi L, Muruganantham N, Vadivelan R. Evaluation of the antipsoriatic activity of Aloe vera leaf extract using a mouse tail model of psoriasis. Phytother Res. 2012;26(4):617-9.

294. Saini M, Goyal PK, Chaudhary G. Anti-tumor activity of Aloe vera against DMBA/croton oil-induced skin papillomagenesis in Swiss albino mice. J Environ Pathol Toxicol Oncol. 2010;29(2):127-35.

295. Chou TH, Liang CH. The molecular effects of aloe-emodin (AE)/liposome-AE on human nonmelanoma skin cancer cells and skin permeation. Chemical research in toxicology. 2009;22(12):2017-28.

296. Wu P, Wang J. Botanical study on Da Qing Ye, Ban Lan Gen and Qing Dai. Shanghai Zhong Yi Yao Da Xue Shanghai Shi Zhong Yi Yao Yan Jiu Yuan Xue Bao. 1996;10(1):50-2.

297. Zhou J, Xie G, Yan X. Vol. 6: Indexes. In: Zhou J, Xie G, Yan X, editors. Encyclopedia of traditional Chinese medicines: Molecular structures, pharmacological activities, natural sources and applications 6. Dordrecht London New York: Springer-Verlag Berlin Heidelberg; 2011. p. 730.

298. Li Q. The chemical constituent of Qingdai. Acta Botanica Sinica. 1987;29(1):67-72.

299. Zhou J, Xie G, Yan X. Vol. 4: Isolated Compounds N-S. In: Zhou J, Xie G, Yan X, editors. Encyclopedia of traditional Chinese medicines: molecular structures, pharmacological activities, natural sources and applications 4. Dordrecht London New York: Springer-Verlag Berlin Heidelberg; 2011. p. 636.

300. Kunikata T, Tatefuji T, Aga H, Iwaki K, Ikeda M, Kurimoto M. Indirubin inhibits inflammatory reactions in delayed-type hypersensitivity. Eur J Pharmacol. 2000;410(1):93–100.

301. Li D, Wu YS, Wang C, Sun Q. Pharmacokinetics research on anti-inflammatory effect and analgesic effect of Indigo Naturalis. Chin J Exp Tradit Med Formul. 2011;17(13):137-40.

302. Suzuki K, Adachi R, Hirayama A, Watanabe H, Otani S, Watanabe Y, et al. Indirubin, a Chinese anti-leukaemia drug, promotes neutrophilic differentiation of human myelocytic leukaemia HL-60 cells. Br J Haematol. 2005;130(5):681–90.

303. Moon M, Lee S, Lee J, Song W, Kim S, Kim J, et al. Synthesis and structure-activity relationships of novel indirubin derivatives as potent anti-proliferative agents with CDK2 inhibitory activities. Bioorg Med Chem. 2006;14(1):237-46.

304. Lee J, Moon M, Min H, Chung H, Park E, Park H, et al. Induction of apoptosis by a novel indirubin-5-nitro-3-monoxime, a CDK inhibitor, in human lung cancer cells. Bioorg Med Chem Lett. 2005;15(17):3948–52.

305. Sirikantaramas S, Asano T, Sudo H, Yamazaki M, Saito K. Camptothecin: therapeutic potential and biotechnology. Curr Pharm Biotechnol. 2007;8(4):196-202.

306. Lorence A, Nessler CL. Camptothecin, over four decades of surprising findings. Phytochemistry. 2004;65(20):2735-49.

307. Lin XR, Huang M. The clinical observation and experimental study of Camptotheca acuminata tincturethe on psoriasis. Chin J Dermatol Venereol. 1982;15(4):210-2.

308. Lin XR, Huang T. Topical camptothecine in treatment of psoriasis. Int J Dermatol. 1988;27(7):475-6.

309. Huang T, Lin X. The effect of camptothecin on proliferation and differentiation of keratinizing epithelium. Chin J Dermatol Venereol. 1996;10(6):325-7, 85.

310. Lin X, Wilkinson DI, Huang T, Farber EM. Experimental studies on topoisomerase inhibitor camptothecin as an antipsoriatic agent. Chin Med J (Engl). 1999;112(6):504-8.

311. Lin JR, Liu XM, Bao YM, Zhang ZY, An LJ, Lin XR. Effect of camptothecin on proliferation, apoptosis and telomerase activation in HaCaT cells. Chin J Dermatol Venereol. 2006;20(10):586-8, 601.

312. Lin J, Liu X, Bao Y, Hou S, An L, Lin X. Effects of isocamptothecin, a novel camptothecin analogue, on proliferation, apoptosis and telomerase activity in HaCaT cells. Exp Dermatol. 2008;17(6):530-6.

313. Muller K, Ziereis K, Gawlik I. The antipsoriatic Mahonia aquifolium and its active constituents; II. antiproliferative activity against cell growth of human keratinocytes. Planta Med. 1995;61(1):74-5.

314. Cernáková M, Kost'álová D, Kettmann V, Plodová M, Tóth J, Drímal J. Potential antimutagenic activity of berberine, a constituent of Mahonia aquifolium. BMC Complement Altern Med. 2002;2(2):1-6.

315. Racková L, Májeková M, Kost'álová D, Stefek M. Antiradical and antioxidant activities of alkaloids isolated from Mahonia aquifolium. Structural aspects. Bioorg Med Chem. 2004;12(17):4709-15.

316. Hajnická V, Kost'álová D, Svecová D, Sochorová R, Fuchsberger N, Tóth J. Effect of Mahonia aquifolium active compounds on interleukin-8 production in the human monocytic cell line THP-1. Planta Med. 2002;68(3):266-8.

317. Rohrer U, Kunz EM, Lenkeit K, Schaffner W, Meyer J. Antimicrobial activity of Mahonia aquifolium and two of its alkaloids against oral bacteria. Schweiz Monatsschr Zahnmed. 2007;117(11):1126-31.

318. Chao J, Lee MS, Amagaya S, Liao JW, Wu JB, Ho LK, et al. Hepatoprotective effect of shidagonglao on acute liver injury induced by carbon tetrachloride. Am J Chin Med. 2009;37(6):1085-97.

319. Zhang L, Ravipati AS, Koyyalamudi SR, Jeong SC, Reddy N, Smith PT, et al. Antioxidant and anti-inflammatory activities of selected medicinal plants containing phenolic and flavonoid compounds. J Agric Food Chem. 2011;59(23):12361-7.

320. Hu W, Yu L, Wang MH. Antioxidant and antiproliferative properties of water extract from Mahonia bealei (Fort.) Carr. leaves. Food Chem Toxicol. 2011;49(4):799-806.

321. Wong BS, Hsiao YC, Lin TW, Chen KS, Chen PN, Kuo WH, et al. The in vitro and in vivo apoptotic effects of Mahonia oiwakensis on human lung cancer cells. Chem Biol Interact. 2009;180(2):165-74.

322. Enk R, Ehehalt R, Graham JE, Bierhaus A, Remppis A, Greten HJ. Differential effect of Rhizoma coptidis and its main alkaloid compound berberine on TNF-alpha induced NFkappaB translocation in human keratinocytes. J Ethnopharmacol. 2007;109(1):170-5.

323. Lou T, Zhang Z, Xi Z, Liu K, Li L, Liu B, et al. Berberine inhibits inflammatory response and ameliorates insulin resistance in hepatocytes. Inflammation. 2011;34(6):659-67.

324. Moon PD, Choi IH, Kim HM. Berberine inhibits the production of thymic stromal lymphopoietin by the blockade of caspase-1/NF-kappaB pathway in mast cells. Int Immunopharmacol. 2011;11(11):1954-9.

325. Vuddanda PR, Chakraborty S, Singh S. Berberine: a potential phytochemical with multispectrum therapeutic activities. Expert Opin Investig Drugs. 2010;19(10):1297-307.

326. Kost'alova D, Kardosova A, Hajnicka V. Effect of Mahonia aquifolium stem bark crude extract and one of its polysaccharide components on production of IL-8. Fitoterapia. 2001;72(7):802-6.

327. Watabe D, Kanno H, Yoshida A, Kurose A, Akasaka T, Sawai T. Adhesion of peripheral blood mononuclear cells and CD4+ T cells from patients with psoriasis to cultured endothelial cells via the interaction between lymphocyte function-associated antigen type 1 and intercellular adhesion molecule 1. Br J Dermatol. 2007;157:259-65.

328. Augustin M, Andrees U, Grimme H, Schopf E, Simon J. Effects of Mahonia aquifolium ointment on the expression of adhesion, proliferation, and activation markers in the skin of patients with psoriasis. Forsch Komplementarmed. 1999;6 Suppl 2:19-21.

329. Zhou J, Xie G, Yan X. Vol. 5: Isolated Compounds T-Z. In: Zhou Jj, Xie G, Yan X, editors. Encyclopedia of traditional Chinese medicines: molecular structures, pharmacological activities, natural sources and applications 5. Dordrecht London New York: Springer-Verlag Berlin Heidelberg; 2011. p. 601.

330. Ding H, Wang R, Gao Y, Zhao Q. The recent development of pharmacological and pharmacokinetic on the ingredients of Sophora flavescens root. Chin Med Res. 1995(4):63-4.

331. Liu G, Dong J, Wang H, Hashi Y, Chen S. Characterization of alkaloids in Sophora flavescens Ait. by high-performance liquid chromatography-electrospray ionization tandem mass spectrometry. J Pharm Biomed Anal. 2011;54(5):1065-72.

332. Kim H, Lee MR, Lee GS, An WG, Cho SI. Effect of Sophora flavescens Aiton extract on degranulation of mast cells and contact dermatitis induced by dinitrofluorobenzene in mice. J Ethnopharmacol. 2012;142(1):253-8.

333. Liu JY, Hu JH, Zhu QG, Li FQ, Wang J, Sun HJ. Effect of matrine on the expression of substance P receptor and inflammatory cytokines production in human skin keratinocytes and fibroblasts. Int Immunopharmacol. 2007;7(6):816-23.

334. Liao J, Zhang B. The anti-inflammatory effect of oxymatrine. J Peking Med Univ. 1988;20(4):313-6.

335. Zheng P, Niu F-L, Liu W-Z, Shi Y, Lu L-G. Anti-inflammatory mechanism of oxymatrine in dextran sulfate sodium-induced colitis of rats. World J Gastroenterol. 2005;11(31):4912-5.

336. Jin JH, Kim JS, Kang SS, Son KH, Chang HW, Kim HP. Anti-inflammatory and anti-arthritic activity of total flavonoids of the roots of Sophora flavescens. J Ethnopharmacol. 2010;127:589–95.

337. Berghe WV, De Naeyer A, Dijsselbloem N, David JP, De Keukeleire D, Haegeman G. Attenuation of ERK/RSK2-driven NFkappaB gene expression and cancer cell proliferation by kurarinone, a lavandulyl flavanone isolated from Sophora flavescens ait. roots. Endocrine, metabolic & immune disorders drug targets. 2011;11(3):247-61.

338. Liu Z, Liu B, Zhang ZT, Zhou TT, Bian HJ, Min MW, et al. A mannose-binding lectin from Sophora flavescens induces apoptosis in HeLa cells. Phytomedicine. 2008;15(10):867-75.

339. Huang ZS, Zhang M, Ma L, Gu LQ. A survey of chemical and pharmacological studies on zicao. Nat Prod Res Dev. 2000;12(1):73-82.

340. Rajasekar S, Park da J, Park C, Park S, Park YH, Kim ST, et al. In vitro and in vivo anticancer effects of Lithospermum erythrorhizon extract on B16F10 murine melanoma. J Ethnopharmacol. 2012;144(2):335-45.

341. Zhang ZQ, Cao XC, Zhang L, Zhu WL. Effect of shikonin, a phytocompound from Lithospermum erythrorhizon, on rat vascular smooth muscle cells proliferation and apoptosis in vitro. Zhonghua Yi Xue Za Zhi. 2005;85(21):1484-8.

342. Zhang Y, Qian RQ, Li PP. Shikonin, an ingredient of Lithospermum erythrorhizon, down-regulates the expression of steroid sulfatase genes in breast cancer cells. Cancer Lett. 2009;284(1):47-54.

343. Yoon Y, Kim YO, Lim NY, Jeon WK, Sung HJ. Shikonin, an ingredient of Lithospermum erythrorhizon induced apoptosis in HL60 human premyelocytic leukemia cell line. Planta Med. 1999;65(6):532-5.

344. Hisa T, Kimura Y, Takada K, Suzuki F, Takigawa M. Shikonin, an ingredient of Lithospermum erythrorhizon, inhibits angiogenesis in vivo and in vitro. Anticancer Res. 1998;18(2A):783-90.

345. Andujar I, Recio MC, Bacelli T, Giner RM, Rios JL. Shikonin reduces oedema induced by phorbol ester by interfering with IkappaBalpha degradation thus inhibiting translocation of NF-kappaB to the nucleus. Br J Pharmacol. 2010;160(2):376-88.

346. Han KY, Kwon TH, Lee TH, Lee SJ, Kim SH, Kim J. Suppressive effects of Lithospermum erythrorhizon extracts on lipopolysaccharide-induced activation of AP-1 and NF-kappaB via mitogen-activated protein kinase pathways in mouse macrophage cells. BMB Rep. 2008;41(4):328-33.

347. Kim EK, Kim EY, Moon PD, Um JY, Kim HM, Lee HS, et al. Lithospermi radix extract inhibits histamine release and production of inflammatory cytokine in mast cells. Biosci Biotechnol Biochem. 2007;71(12):2886-92.

348. Lee JH, Jung KM, Bae IH, Cho S, Seo DB, Lee SJ, et al. Anti-inflammatory and barrier protecting effect of Lithospermum erythrorhizon extracts in chronic oxazolone-induced murine atopic dermatitis. J Dermatol Sci. 2009;56(1):64-6.

349. Kim J, Kim H, Jeong do H, Kim SH, Park SK, Cho Y. Comparative effect of gromwell (Lithospermum erythrorhizon) extract and borage oil on reversing epidermal hyperproliferation in guinea pigs. Biosci Biotechnol Biochem. 2006;70(9):2086-95.

350. Kim J, Kim Y, Seo D, Kim S, Lee S, Cho Y. Oral supplementation of Lithospermum erythrorhizon prevents the development of atopic dermatitis with reducing ceramide degradation in the epidermis of NC/Nga mice. Phytother Res. 2009;23(9):1250-6.

351. Ishida T, Sakaguchi I. Protection of human keratinocytes from UVB-induced inflammation using root extract of Lithospermum erythrorhizon. Biol Pharm Bull. 2007;30(5):928-34.

352. Ozaki Y, Sakaguchi I, Tujimura M, Ikeda N, Nakayama M, Kato Y, et al. Study of the accelerating effect of shikonin and alkannin on the proliferation of granulation tissue in rats. Biol Pharm Bull. 1998;21(4):366-70.

353. Kim H, Kim J, Park J, Kim SH, Uchida Y, Holleran WM, et al. Water extract of gromwell (Lithospermum erythrorhizon) enhances migration of human keratinocytes and dermal fibroblasts with increased lipid synthesis in an in vitro wound scratch model. Skin Pharmacol Physiol. 2012;25(2):57-64.

354. Lian Q. Development of chemical constitutes and pharmaceautical action on Cnidium monnieri seed. Zhong Yao Cai. 2003;26(2):141-3.

355. Liao P-C, Chien S-C, Ho C-L, Wang EI-C, Lee S-C, Kuo Y-H, et al. Osthole regulates inflammatory mediator expression through modulating NF-KB, Mitogen-Activated Protein Kinases, Protein Kinase C, and Reactive Oxygen Species. J Agric Food Chem. 2010;58:10445–51.

356. Tse W-P, Che C-T, Liu K, Lin Z-X. Evaluation of the anti-proliferative properties of selected psoriasis-treating Chinese medicines on cultured HaCaT cells. J Ethnopharmacol. 2006;108:133–41.

357. Zimecki M, Artym J, Cisowski W, Mazol I, W³odarczyk M, Gleñsk M. Immunomodulatory and anti-inflammatory activity of selected osthole derivatives. Z Naturforsch C. 2009;64(5-6):361-8.

358. Yamaguchi-Miyamoto T, Kawasuji T, Kuraishi Y, SuzukI H. Anitpruritic effects of Sophora flavescens on acute and chronic ich-related responses in mice. Biol Pharm Bull. 2003;16(5):722-4.

359. Gao X, Zhao P-H, Hu J-F. Chemical constituents of plants from the Genus dictamnus. Chem Biodivers. 2011;8:1234-44.

360. Xu Q, Yuan K, Lu J, Wang R, Wu F. A new strategy for regulating the immunological liver injury - effectiveness of DTH-inhibiting agents on DTH-induced liver injury to picryl chloride. Pharmacol Res. 1997;36(5):401-9.

361. Kim J-H, Park Y-M, Shin J-S, Park SJ, Choi J-H, Jung H-J, et al. Fraxinellone inhibits lipopolysaccharide-induced inducible nitric oxide synthase and cyclooxygenase-2 expression by negatively regulating nuclear factor-kappa B in RAW 264.7 macrophages cells. Biol Pharm Bull. 2009;32(6):1062—8.

362. Chang J, Xuan L-J, Xu Y-M, Zhang J-S. Seven new Sesquiterpene glycosides from the root bark of Dictamnus dasycarpus. J Nat Prod. 2001;64:935-8.

363. Jiang S, Nakano Y, Rahman MA, Yatsuzuka R, Kamei C. Effects of a Dictamnus dasycarpus T. extract on allergic models in mice. Biosci Biotechnol Biochem. 2008;72(3):660-5.

364. Chen L, Su J, Li L, Li B, Li W. A new source of natural D-borneol and its characteristic. J Med Plant Res. 2011;5(15):3440-7.

365. Dai JP, Chen J, Bei YF, Han BX, Wang S. Influence of borneol on primary mice oral fibroblasts: a penetration enhancer may be used in oral submucous fibrosis. J Oral Pathol Med. 2009;38(3):276-81.

366. Cui Y, Li L, Zhang L, Li J, Gu J, Gong H, et al. Enhancement and mechanism of transdermal absorption of terpene-induced propranolol hydrochloride. Arch Pharm Res. 2011;34(9):1477-85.

367. Gao ZS, Wang L, Zhang M. Effects of penetration enhancers on curcumin transdermal drug delivery. Zhong Yao Cai. 2012;35(1):141-4.

368. Zhang CF, Zhan W, Yang ZL, Wang YL. Impacts of bicyclo-monoterpene enhancers on transdermal delivery of ligustrazine. Yao Xue Xue Bao. 2010;45(11):1452-8.

369. Lu Y, Du S, Yao Z, Zhao P, Zhai Y. Study on natural borneol and synthetic borneol affecting mucosal permeability of Gardenia extract. Zhongguo Zhong Yao Za Zhi. 2009;34(10):1207-10.

370. Mai LM, Lin CY, Chen CY, Tsai YC. Synergistic effect of bismuth subgallate and borneol, the major components of Sulbogin, on the healing of skin wound. Biomaterials. 2003;24(18):3005-12.

371. Serena T, Parnall LK, Knox C, Vargo J, Oliver A, Merry S, et al. Bismuth subgallate/borneol (suile) is superior to bacitracin in the human forearm biopsy model for acute wound healing. Adv Skin Wound Care. 2007;20(9 Pt 1):485-92.

372. Racz E, Prens EP. Molecular pathophysiology of psoriasis and molecular targets of antipsoriatic therapy. Expert Rev Mol Med. 2009;11:e38.

373. Warren RB, Griffiths CE. Systemic therapies for psoriasis: methotrexate, retinoids, and cyclosporine. Clin Dermatol. 2008;26(5):438-47.

374. Zheng CJ, Han LY, Yap CW, Ji ZL, Cao ZW, Chen YZ. Therapeutic targets: progress of their exploration and investigation of their characteristics. Pharmacol Rev. 2006;58(2):259-79.

375. Ehrman TM, Barlow DJ, Hylands PJ. In silico search for multi-target anti-inflammatories in Chinese herbs and formulas. Bioorg Med Chem. 2010;18(6):2204-18.

376. Jiang C-Y, Tan Y, Lv C, Li L, Li J, Zhang G-Z. Prediction of the molecular mechanism of Rehmannia glutinosa treatment for psoriasis based on network pharmacology. Chinese Journal of Basic Medicine in Traditional Chinese Medicine. 2013;19(4):404-7.

377. Liu X, Wu WY, Jiang BH, Yang M, Guo DA. Pharmacological tools for the development of traditional Chinese medicine. Trends Pharmacol Sci. 2013;34(11):620-8.

378. Lu C, Deng J, Li L, Wang D, Li G. Application of metabolomics on diagnosis and treatment of patients with psoriasis in traditional Chinese medicine. Biochim Biophys Acta. 2014;1844(1 Pt B):280-8.

379. Mandal V, Gopal V, Mandal SC. An inside to the better understanding of the ethnobotanical route to drug discovery -the need of the hour. Nat Prod Commun. 2012;7(11):1551-4.

380. Yang HJ, Shen D, Xu HY, Lu P. A new strategy in drug design of Chinese medicine: theory, method and techniques. Chin J Integr Med. 2012;18(11):803-6.

381. Bayliffe AI, Brigandi RA, Wilkins HJ, Levick MP. Emerging therapeutic targets in psoriasis. Curr Opin Pharmacol. 2004;4(3):306-10.

382. Raychaudhuri SP, Raychaudhuri SK. Biologics: target-specific treatment of systemic and cutaneous autoimmune diseases. Indian J Dermatol. 2009;54(2):100-9.

383. Breinbauer R, Manger M, Scheck M, Waldmann H. Natural product guided compound library development. Curr Med Chem. 2002;9(23):2129-45.

384. Fang X, Shao L, Zhang H, Wang S. CHMIS-C: A comprehensive herbal medicine information system for cancer. J Med Chem. 2005;48(5):1481-8.

385. Ehrman TM, Barlow DJ, Hylands PJ. Phytochemical databases of Chinese herbal constituents and bioactive plant compounds with known target specificities. J Chem Inf Model. 2007;47(2):254-63.

386. Ye H, Ye L, Kang H, Zhang D, Tao L, Tang K, et al. HIT: linking herbal active ingredients to targets. Nucleic Acids Res. 2011;39(Database issue):D1055-9.

387. Zhou J, Xie G, Yan X. Vol. 1: Isolated Compounds A-C. In: Zhou Jj, Xie G, Yan X, editors. Encyclopedia of traditional Chinese medicines: molecular structures, pharmacological activities, natural sources and applications 1. Dordrecht London New York: Springer-Verlag Berlin Heidelberg; 2011. p. 557.

388. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, et al. DrugBank 3.0: A comprehensive resource for 'omics' research on drugs. Nucleic Acids Res. 2011;39(Database issue):D1035-41.

389. Mi H, Muruganujan A, Casagrande JT, Thomas PD. Large-scale gene function analysis with the PANTHER classification system. Nat Protoc. 2013;8(8):1551-66.

390. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, et al. DrugBank: A comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006;34(Database issue):D668-72.

391. Stark K, Torma H, Oliw EH. Co-localization of COX-2, CYP4F8, and mPGES-1 in epidermis with prominent expression of CYP4F8 mRNA in psoriatic lesions. Prostaglandins Other Lipid Mediat. 2006;79(1-2):114-25.

392. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood. 2012;119(3):651-65.

393. Kontermann RE, Scheurich P, Pfizenmaier K. Antagonists of TNF action: Clinical experience and new developments. Expert Opin Drug Discov. 2009;4(3):279-92.

394. Cole SP. Targeting multidrug resistance protein 1 (MRP1, ABCC1): Past, present, and future. Annu Rev Pharmacol Toxicol. 2014;54:95-117.

395. Lau D, Baldus S. Myeloperoxidase and its contributory role in inflammatory vascular disease. Pharmacol Ther. 2006;111(1):16-26.

396. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2005;25(6):1102-11.

397. Skrzydlewska E, Sulkowska M, Koda M, Sulkowski S. Proteolytic-antiproteolytic balance and its regulation in carcinogenesis. World J Gastroenterol. 2005;11(9):1251-66.

398. Nebert DW, Russell DW. Clinical importance of the cytochromes P450. Lancet. 2002;360(9340):1155-62.

399. Ahmad N, Mukhtar H. Cytochrome p450: A target for drug development for skin diseases. J Invest Dermatol. 2004;123(3):417-25.

400. Zhou X, Chan K, Yeung JHK. Herb-drug interactions with Danshen (Salvia miltiorrhiza): A review on the role of cytochrome P450 enzymes. Drug Metab Drug Interact. 2012;27(1):9-18.

401. Lan T, Wu T, Chen C, Chen X, Hao J, Huang J, et al. Berberine attenuates high glucose-induced proliferation and extracellular matrix accumulation in mesangial cells: Involvement of suppression of cell cycle progression and NF-kappaB/AP-1 pathways. Mol Cell Endocrinol. 2014.

402. Mi H, Thomas P. PANTHER pathway: An ontology-based pathway database coupled with data analysis tools. Methods Mol Biol. 2009;563:123-40.

403. Kanehisa M, Goto S, Furumichi M, Tanabe M, Hirakawa M. KEGG for representation and analysis of molecular networks involving diseases and drugs. Nucleic Acids Res. 2010;38(Database issue):D355-60.

404. Kanehisa M, Goto S, Sato Y, Furumichi M, Tanabe M. KEGG for integration and interpretation of large-scale molecular data sets. Nucleic Acids Res. 2012;40(Database issue):D109-14.

405. Correia S, Alves MG, Oliveira PF, Alves MR, van Pelt AM, Cavaco JE, et al. Transgenic overexpression of regucalcin leads to suppression of thapsigargin- and actinomycin D-induced apoptosis in the testis by modulation of apoptotic pathways. Andrology. 2014.

406. Kocak M, Bozdogan O, Erkek E, Atasoy P, Birol A. Examination of Bcl-2, Bcl-X and bax protein expression in psoriasis. Int J Dermatol. 2003;42(10):789-93.

407. Tsuchiya A, Kanno T, Shimizu T, Nakao S, Tanaka A, Tabata C, et al. A novel PP2A enhancer induces caspase-independent apoptosis of MKN28 gastric cancer cells with high MEK activity. Cancer Lett. 2014.

408. Mantawy EM, El-Bakly WM, Esmat A, Badr AM, El-Demerdash E. Chrysin alleviates acute doxorubicin cardiotoxicity in rats via suppression of oxidative stress, inflammation and apoptosis. Eur J Pharmacol. 2014.

409. Crawshaw AA, Griffiths CE, Young HS. Investigational VEGF antagonists for psoriasis. Expert Opin Investig Drugs. 2012;21(1):33-43.

410. Huang H, Zhang P, Wang Z, Tang F, Jiang Z. Activation of endothelin-1 receptor signaling pathways is associated with neointima formation, neoangiogenesis and irreversible pulmonary artery hypertension in patients with congenital heart disease. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(6):1463-71.

411. Liu CP, Hsieh CH, Wu BN, Yeh JL, Dai ZK, Chai CY, et al. Inhaled KMUP-1 prevents allergic pulmonary vascular inflammation and remodeling via NO and suppressed MMP-9 and ICAM-1/VCAM-1. Inflamm Allergy Drug Targets. 2012;11(4):251-61.

412. Pandya NM, Dhalla NS, Santani DD. Angiogenesis--a new target for future therapy. Vascul Pharmacol. 2006;44(5):265-74.

413. Xiang B, Zhang G, Guo L, Li XA, Morris AJ, Daugherty A, et al. Platelets protect from septic shock by inhibiting macrophage-dependent inflammation via the cyclooxygenase 1 signalling pathway. Nat Commun. 2013;4:2657.

414. Hanson J, Gille A, Offermanns S. Role of HCA(2) (GPR109A) in nicotinic acid and fumaric acid ester-induced effects on the skin. Pharmacol Ther. 2012;136(1):1-7.

415. Krueger G, Callis K. Potential of tumor necrosis factor inhibitors in psoriasis and psoriatic arthritis. Arch Dermatol. 2004;140(2):218-25.

416. Pradelli LA, Beneteau M, Ricci JE. Mitochondrial control of caspase-dependent and -independent cell death. Cellular and molecular life sciences: CMLS. 2010;67(10):1589-97.

417. Batinac T, Zamolo G, Hadzisejdic I, Zauhar G, Brumini G, Ruzic A, et al. Expression of Bcl-2 family proteins in psoriasis. Croat Med J. 2007;48(3):319-26.

418. Pathak AK, Bhutani M, Nair AS, Ahn KS, Chakraborty A, Kadara H, et al. Ursolic acid inhibits STAT3 activation pathway leading to suppression of proliferation and chemosensitization of human multiple myeloma cells. Molecular cancer research: MCR. 2007;5(9):943-55.

419. Hsu YL, Kuo PL, Lin CC. Proliferative inhibition, cell-cycle dysregulation, and induction of apoptosis by ursolic acid in human non-small cell lung cancer A549 cells. Life Sci. 2004;75(19):2303-16.

420. Choi EJ, Bae SM, Ahn WS. Antiproliferative effects of quercetin through cell cycle arrest and apoptosis in human breast cancer MDA-MB-453 cells. Arch Pharm Res. 2008;31(10):1281-5.

421. Vijayababu MR, Arunkumar A, Kanagaraj P, Arunakaran J. Effects of quercetin on insulin-like growth factors (IGFs) and their binding protein-3 (IGFBP-3) secretion and induction of apoptosis in human prostate cancer cells. J Carcinog. 2006;5:10.

422. Choi YH, Baek JH, Yoo MA, Chung HY, Kim ND, Kim KW. Induction of apoptosis by ursolic acid through activation of caspases and down-regulation of c-IAPs in human prostate epithelial cells. Int J Oncol. 2000;17(3):565-71.

423. Andersson D, Liu JJ, Nilsson A, Duan RD. Ursolic acid inhibits proliferation and stimulates apoptosis in HT29 cells following activation of alkaline sphingomyelinase. Anticancer Res. 2003;23(4):3317-22.

424. Kim KH, Seo HS, Choi HS, Choi I, Shin YC, Ko SG. Induction of apoptotic cell death by ursolic acid through mitochondrial death pathway and extrinsic death receptor pathway in MDA-MB-231 cells. Arch Pharm Res. 2011;34(8):1363-72.

425. Baldwin AS. Regulation of cell death and autophagy by IKK and NF-kappaB: critical mechanisms in immune function and cancer. Immunol Rev. 2012;246(1):327-45.

426. Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death--a new approach to cancer therapy. J Clin Invest. 2005;115(10):2625-32.

427. Priyadarsini RV, Nagini S. Quercetin suppresses cytochrome P450 mediated ROS generation and NFkappaB activation to inhibit the development of 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinomas. Free Radic Res. 2012;46(1):41-9.

428. Boots AW, Wilms LC, Swennen ELR, Kleinjans JCS, Bast A, Haenen GRMM. In vitro and ex vivo anti-inflammatory activity of quercetin in healthy volunteers. Nutrition. 2008;24:703–10.

429. Avramidis G, Kruger-Krasagakis S, Krasagakis K, Fragiadaki I, Kokolakis G, Tosca A. The role of endothelial cell apoptosis in the effect of etanercept in psoriasis. Br J Dermatol. 2010;163(5):928-34.

430. Song W, Sun Q, Dong Z, Spencer DM, Nunez G, Nor JE. Antiangiogenic gene therapy: Disruption of neovascular networks mediated by inducible caspase-9 delivered with a transcriptionally targeted adenoviral vector. Gene Ther. 2005;12(4):320-9.

431. Cao HH, Tse AK, Kwan HY, Yu H, Cheng CY, Su T, et al. Quercetin exerts anti-melanoma activities and inhibits STAT3 signaling. Biochem Pharmacol. 2014;87(3):424-34.

432. Pratheeshkumar P, Budhraja A, Son YO, Wang X, Zhang Z, Ding S, et al. Quercetin inhibits angiogenesis mediated human prostate tumor growth by targeting VEGFR- 2 regulated AKT/mTOR/P70S6K signaling pathways. PloS one. 2012;7(10):e47516.

433. Yang PY, Rui YC, Zhang L, Li TJ, Qiu Y, Wang JS, et al. Expression of vascular endothelial growth factor in U937 foam cells and the inhibitory effect of drugs. Yao Xue Xue Bao. 2002;37(2):86-9.

434. Wang Y, Xu F, Chen J, Shen X, Deng Y, Xu L, et al. Matrix metalloproteinase-9 induces cardiac fibroblast migration, collagen and cytokine secretion: Inhibition by salvianolic acid B from Salvia miltiorrhiza. Phytomedicine. 2011;19(1):13-9.

435. Jachak SM. Cyclooxygenase inhibitory natural products: current status. Curr Med Chem. 2006;13(6):659-78.

436. Hao Y, Xie T, Korotcov A, Zhou Y, Pang X, Shan L, et al. Salvianolic acid B inhibits growth of head and neck squamous cell carcinoma in vitro and in vivo via cyclooxygenase-2 and apoptotic pathways. Int J Cancer. 2009;124(9):2200-9.

437. Kowalczyk MC, Junco JJ, Kowalczyk P, Tolstykh O, Hanausek M, Slaga TJ, et al. Effects of combined phytochemicals on skin tumorigenesis in SENCAR mice. International journal of oncology. 2013;43(3):911-8.

438. Luqman S, Pezzuto JM. NFkappaB: A promising target for natural products in cancer chemoprevention. Phytother Res. 2010;24(7):949-63.

439. Kleemann R, Verschuren L, Morrison M, Zadelaar S, van Erk MJ, Wielinga PY, et al. Anti-inflammatory, anti-proliferative and anti-atherosclerotic effects of quercetin in human in vitro and in vivo models. Atherosclerosis. 2011;218(1):44-52.

440. Potapovich AI, Lulli D, Fidanza P, Kostyuk VA, De Luca C, Pastore S, et al. Plant polyphenols differentially modulate inflammatory responses of human keratinocytes by interfering with activation of transcription factors NFkappaB and AhR and EGFR-ERK pathway. Toxicol Appl Pharmacol. 2011;255(2):138-49.

441. Kahraman A, Cakar H, Koken T. The protective effect of quercetin on long-term alcohol consumption-induced oxidative stress. Mol Biol Rep. 2012;39(3):2789-94.

442. Manu KA, Kuttan G. Ursolic acid induces apoptosis by activating p53 and caspase-3 gene expressions and suppressing NF-kappaB mediated activation of bcl-2 in B16F-10 melanoma cells. Int Immunopharmacol. 2008;8(7):974-81.

443. Cho JM, Chang SY, Kim DB, Needs PW, Jo YH, Kim MJ. Effects of physiological quercetin metabolites on interleukin-1beta-induced inducible NOS expression. J Nutr Biochem. 2012;23(11):1394-402.

444. Jin HB, Yang YB, Song YL, Zhang YC, Li YR. Protective roles of quercetin in acute myocardial ischemia and reperfusion injury in rats. Mol Biol Rep. 2012;39(12):11005-9.

445. Tai ZF, Zhang GL, Wang F. Identification of small molecule activators of the janus kinase/signal transducer and activator of transcription pathway using a cell-based screen. Biol Pharm Bull. 2012;35(1):65-71.

446. Senggunprai L, Kukongviriyapan V, Prawan A, Kukongviriyapan U. Quercetin and EGCG exhibit chemopreventive effects in cholangiocarcinoma Cells via suppression of JAK/STAT signaling Pathway. Phytother Res. 2013.

447. Zhou Y, Li JS, Zhang X, Wu YJ, Huang K, Zheng L. Ursolic acid inhibits early lesions of diabetic nephropathy. Int J Mol Med. 2010;26(4):565-70.

448. Dubrac S, Schmuth M. PPAR-alpha in cutaneous inflammation. Dermatoendocrinol. 2011;3(1):23-6.

449. Mehta NN, Li K, Szapary P, Krueger J, Brodmerkel C. Modulation of cardiometabolic pathways in skin and serum from patients with psoriasis. J Transl Med. 2013;11:194.

450. Wilkinson AS, Monteith GR, Shaw PN, Lin CN, Gidley MJ, Roberts-Thomson SJ. Effects of the Mango components mangiferin and quercetin and the putative mangiferin metabolite norathyriol on the transactivation of peroxisome proliferator-activated receptor isoforms. J Agric Food Chem. 2008;56(9):3037-42.

451. Chao PY, Lin KH, Chiu CC, Yang YY, Huang MY, Yang CM. Inhibitive effects of mulberry leaf-related extracts on cell adhesion and inflammatory response in human aortic endothelial cells. Evid Based Complement Alternat Med. 2013;2013:267217.

452. Lu X, Du J, Liang J, Zhu X, Yang Y, Xu J. Transcriptional regulatory network for psoriasis. J Dermatol. 2013;40(1):48-53.

453. Manriquez Moreno JJ. Evidence-based dermatology: A synopsis. Actas Dermosifiliogr. 2009;100(2):89-99.

454. Williams H. Evidence-Based dermatology: Everyone's business. Am J Clin Dermatol. 2011;12(6):357-9.

455. Breinbauer R, Vetter IR, Waldmann H. From protein domains to drug candidates-natural products as guiding principles in the design and synthesis of compound libraries. Angewandte Chemie (International ed in English). 2002;41(16):2879-90.

456. Lu A, Liu B, Liu H, Zhou J, Xie G. A Traditional Chinese Medicine plant–compound database and its application for searching. Internet Electronic Journal of Molecular Design. 2004;3(10):672–83.

457. Villanova F, Di Meglio P, Nestle FO. Biomarkers in psoriasis and psoriatic arthritis. Ann Rheum Dis. 2013;72 Suppl 2:ii104-10.

458. Xie W, Du L. Diabetes is an inflammatory disease: evidence from traditional Chinese medicines. Diabetes Obes Metab. 2011;13(4):289-301.

459. Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. J Clin Invest. 2006;116(5):1218-22.

460. Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol. 2013;34(4):174-81.

461. Tan X, Feldman SR, Chang J, Balkrishnan R. Topical drug delivery systems in dermatology: A review of patient adherence issues. Expert Opin Drug Deliv. 2012;9(10):1263-71.

462. Seavey MM, Dobrzanski P. The many faces of Janus kinase. Biochem Pharmacol. 2012;83(9):1136-45.

463. Svensson L, Ropke MA, Norsgaard H. Psoriasis drug discovery: Methods for evaluation of potential drug candidates. Expert Opin Drug Discov. 2012;7(1):49-61.

464. Fishman P, Bar-Yehuda S, Liang BT, Jacobson KA. Pharmacological and therapeutic effects of A3 adenosine receptor agonists. Drug Discov Today. 2012;17(7-8):359-66.

465. Barker CL, McHale MT, Gillies AK, Waller J, Pearce DM, Osborne J, et al. The development and characterization of an in vitro model of psoriasis. J Invest Dermatol. 2004;123(5):892-901.

466. Bladon PT, Taylor M, Wood EJ, Cunliffe WJ. Effect of crude coal tar in the mouse-tail model of psoriasis. Arch Dermatol Res. 1985;277(2):121-5.

467. Singhal M, Kansara N. Cassia tora L. Creams inhibit psoriasis in mouse tail model. Pharmaceutical Crops. 2012;3:1-6.

468. Carrier Y, Ma HL, Ramon HE, Napierata L, Small C, O'Toole M, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: Implications in psoriasis pathogenesis. J Invest Dermatol. 2011;131(12):2428-37.

469. Han L. Reflection of the animal models on psoriatic pharmacodynamic and its application in the new Chinese herbal medicine research. Pharmacology and Clinical of Chinese Materia Medica. 2006;22(6):73-5.

470. Hirotsu C, Rydlewski M, Araujo MS, Tufik S, Andersen ML. Sleep loss and cytokines levels in an experimental model of psoriasis. PloS one. 2012;7(11):e51183.

471. Bracke S, Carretero M, Guerrero-Aspizua S, Desmet E, Illera N, Navarro M, et al. Targeted silencing of DEFB4 in a bio-engineered skin-humanised mouse model for psoriasis: Development of siRNA SECosome-based novel therapies. Exp Dermatol. 2014.

472. Song P, Lysvand H, Yuhe Y, Liu W, Iversen OJ. Expression of the psoriasis-associated antigen, Pso p27, is inhibited by traditional Chinese medicine. J Ethnopharmacol. 2010;127(1):171-4.

473. Suarez-Farinas M, Li K, Fuentes-Duculan J, Hayden K, Brodmerkel C, Krueger JG. Expanding the psoriasis disease profile: Interrogation of the skin and serum of patients with moderate-to-severe psoriasis. J Invest Dermatol. 2012;132(11):2552-64.

Appendix 1 Biological targets list for Bai hua she she cao (*Oldenlandia diffusa*)

Species	Chinese	Compound name	Compound ID	Target ID	Target name
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0026	72 kDa type IV collagenase
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0185	Acetylcholinesterase
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0018	Apoptosis regulator BAX
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0018	Apoptosis regulator BAX
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0013	Apoptosis regulator Bcl-2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0013	Apoptosis regulator Bcl-2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0202	Baculoviral IAP repeat-containing protein 5
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0014	Bcl-2-like protein 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0213	Caspase-1
O. diffusa	白花蛇舌草	Oleanolic acid	16050	T0045	Caspase-3
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0045	Caspase-3
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0045	Caspase-3
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0060	Caspase-8
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0060	Caspase-8
O. diffusa	白花蛇舌草	Oleanolic acid	16050	T0019	Caspase-9
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0019	Caspase-9
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0019	Caspase-9
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0207	Cathepsin B
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0034	Cell division protein kinase 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0035	Cell division protein kinase 4
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0041	Cell division protein kinase 6
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0046	Cellular tumor antigen p53

O. diffusa	白花蛇舌草	Ursolic acid	22270	T0200	C-Jun-amino-terminal kinase-interacting protein 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0201	C-Jun-amino-terminal kinase-interacting protein 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0196	Cyclic AMP-dependent transcription factor ATF-2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0157	Cyclic AMP-responsive element-binding protein 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0016	Cyclin-dependent kinase inhibitor 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0205	Dual oxidase 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0310	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0174	E-selectin
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0061	Fatty acid synthase
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0012	G1/S-specific cyclin-D1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0211	G1/S-specific cyclin-D2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0197	Granulocyte-macrophage colony-stimulating factor
O. diffusa	白花蛇舌草	Oleanolic acid	16050	T0135	Heme oxygenase 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0116	Heparin-binding growth factor 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0182	Induced myeloid leukemia cell differentiation protein Mcl-1
O. diffusa	白花蛇舌草	Oleanolic acid	16050	T0152	Intercellular adhesion molecule 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0152	Intercellular adhesion molecule 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0156	Interleukin-1 beta
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0039	Interleukin-6
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0086	Interstitial collagenase
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0210	Lipopolysaccharide-induced tumor necrosis factor-alpha factor
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0027	Matrix metalloproteinase-9
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0826	Microtubule-associated protein 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0052	Mitogen-activated protein kinase 8

O. diffusa	白花蛇舌草	Oleanolic acid	16050	T0323	NAD(P)H dehydrogenase [quinone] 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0204	Neuromodulin
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0055	NF-kappa-B inhibitor alpha
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0206	Nitric oxide synthase, endothelial
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0040	Nitric oxide synthase, inducible
O. diffusa	白花蛇舌草	Oleanolic acid	16050	T1106	Pancreatic alpha-amylase
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0209	Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0198	Platelet endothelial cell adhesion molecule
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0099	Probable E3 ubiquitin-protein ligase HERC5
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0178	Prostaglandin E2 receptor EP3 subtype
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0179	Prostaglandin G/H synthase 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0054	Prostaglandin G/H synthase 2
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0077	Protein kinase C alpha type
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0195	Protein kinase C gamma type
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0015	Proto-oncogene c-Fos
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0199	Proto-oncogene tyrosine-protein kinase Src
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0379	Serum paraoxonase/arylesterase 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0008	Signal transducer and activator of transcription 3
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0087	Stromelysin-1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0146	Stromelysin-2
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0038	Transcription factor AP-1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0038	Transcription factor AP-1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0002	Transcription factor p65
O. diffusa	白花蛇舌草	Stigmasterol	20369	T0226	Transforming growth factor beta-1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0037	Tumor necrosis factor

O. diffusa	白花蛇舌草	Ursolic acid	22270	T0212	Tumor necrosis factor ligand superfamily member 6
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0208	Tyrosine-protein phosphatase non-receptor type 1
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0203	Tyrosine-protein phosphatase non-receptor type 6
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0025	Urokinase-type plasminogen activator
O. diffusa	白花蛇舌草	Ursolic acid	22270	T0010	Vascular endothelial growth factor A
O. diffusa	白花蛇舌草	5-O-p-Methoxy cinnamoyl scandoside methyl ester	13895	NA	
O. diffusa	白花蛇舌草	6-O-E-p-Coumaroyl scandoside methyl ester	4185	NA	
O. diffusa	白花蛇舌草	6-O-Z-p-Coumaroyl scandoside methyl ester	4186	NA	
O. diffusa	白花蛇舌草	6-O-Z-p-Methoxycinnamoyl scandoside methyl ester	13894	NA	
O. diffusa	白花蛇舌草	Asperulosidic acid	1894	NA	
O. diffusa	白花蛇舌草	Kaempferol 3-O-[(6-O-feruloyl)-β-D-glucopyranosyl-(1→2)-β-Dgalactopyranoside]	12046	NA	
O. diffusa	白花蛇舌草	Panasenoside	16587	NA	
O. diffusa	白花蛇舌草	Quercetin-3-O-[(6-O-feruloyl)-β-D-glucopyranosyl-(1→2)-β-Dgalactopyranoside]	18354	NA	
O. diffusa	白花蛇舌草	Quercetin-3-O-[2-O-(6-O-E-feruloyl)-β-D-glucopyranosyl]-β-D -glucopyranoside	18355	NA	
O. diffusa	白花蛇舌草	Quercetin-3-O-[2-O-(6-O-E-sinapoyl)-β-D-glucopyranosyl]-β-Dglucopyranoside	18396	NA	
O. diffusa	白花蛇舌草	Quercetin-3-O-[β-D-glucopyranosyl-(1→2)-β-D-galactopyrano- side]	18362	NA	

Appendix 2 Biological target list for Di huang (*Rehmannia glutinosa, R. glutinosa var. purpurea*)

Species	Chinesee	Compound name	Compound ID	Target ID	Target name
R. glutinosa	干地黄	Cinnamic acid	3695	T0185	Acetylcholinesterase
R. glutinosa	干地黄	Cinnamic acid	3695	T0881	Aldo-keto reductase family 1 member C1
R. glutinosa	干地黄	Cinnamic acid	3695	T0324	Alpha-1A adrenergic receptor
R. glutinosa	干地黄	Raffinose	18526	T1296	Alpha-galactosidase A
R. glutinosa	干地黄	Cinnamic acid	3695	T0440	Alpha-synuclein
R. glutinosa	干地黄	Cinnamic acid	3695	T0959	Antizyme inhibitor 1
R. glutinosa	干地黄	Aucubin	2004	T0018	Apoptosis regulator BAX
R. glutinosa	干地黄	Cinnamic acid	3695	T0018	Apoptosis regulator BAX
R. glutinosa	干地黄	Stigmasterol	20369	T0018	Apoptosis regulator BAX
R. glutinosa	干地黄	Aucubin	2004	T0013	Apoptosis regulator Bcl-2
R. glutinosa	干地黄	Catalpol	3306	T0013	Apoptosis regulator Bcl-2
R. glutinosa	熟地黄	Catalpol	3306	T0013	Apoptosis regulator Bcl-2
R. glutinosa	鲜地黄(生地)	Catalpol	3306	T0013	Apoptosis regulator Bcl-2
R. glutinosa	干地黄	Geniposide	8276	T0013	Apoptosis regulator Bcl-2
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0013	Apoptosis regulator Bcl-2
R. glutinosa	干地黄	Stigmasterol	20369	T0013	Apoptosis regulator Bcl-2
R. glutinosa	干地黄	Cinnamic acid	3695	T0279	Arachidonate 5-lipoxygenase
R. glutinosa	干地黄	Catalpol	3306	T0045	Caspase-3
R. glutinosa	熟地黄	Catalpol	3306	T0045	Caspase-3
R. glutinosa	鲜地黄(生地)	Catalpol	3306	T0045	Caspase-3
R. glutinosa	干地黄	Cinnamic acid	3695	T0045	Caspase-3

R. glutinosa	干地黄	Cinnamic acid	3695	T0045	Caspase-3
R. glutinosa	干地黄	Stigmasterol	20369	T0045	Caspase-3
R. glutinosa	干地黄	Succinic acid	20444	T0045	Caspase-3
R. glutinosa	干地黄	Stigmasterol	20369	T0060	Caspase-8
R. glutinosa	干地黄	Stigmasterol	20369	T0019	Caspase-9
R. glutinosa	干地黄	Cinnamic acid	3695	T0438	C-C chemokine receptor type 3
R. glutinosa	干地黄	Cinnamic acid	3695	T0546	C-C motif chemokine 16
R. glutinosa	干地黄	Cinnamic acid	3695	T0167	C-C motif chemokine 2
R. glutinosa	干地黄	Cinnamic acid	3695	T0434	C-C motif chemokine 3
R. glutinosa	干地黄	Cinnamic acid	3695	T0308	Choline O-acetyltransferase
R. glutinosa	干地黄	Hexadecanoic acid	9486	T1102	Choline-phosphate cytidylyltransferase A
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0267	Collagen alpha-1(I) chain
R. glutinosa	干地黄	Cinnamic acid	3695	T0580	Complement C3
R. glutinosa	干地黄	Cinnamic acid	3695	T1243	Complement C5
R. glutinosa	干地黄	Cinnamic acid	3695	T0016	Cyclin-dependent kinase inhibitor 1
R. glutinosa	干地黄	Cinnamic acid	3695	T0150	Cytochrome P450 1A1
R. glutinosa	干地黄	Aucubin	2004	T1266	DNA-directed RNA polymerase II subunit RPB1
R. glutinosa	干地黄	Lauric acid	12569	T0205	Dual oxidase 2
R. glutinosa	干地黄	Stearic acid	20280	T0310	Ectonucleotide pyrophosphatase/ phosphodiesterase family member 7
R. glutinosa	干地黄	Cinnamic acid	3695	T0437	Eotaxin
R. glutinosa	干地黄	Cinnamic acid	3695	T0017	Eukaryotic translation initiation factor 6
R. glutinosa	干地黄	Caprylic acid	3140	T0633	Fatty acid-binding protein, liver
R. glutinosa	干地黄	Cinnamic acid	3695	T0246	G1/S-specific cyclin-D3
R. glutinosa	干地黄	Cinnamic acid	3695	T0215	Gamma-glutamyltransferase 5
R. glutinosa	干地黄	Cinnamic acid	3695	T0346	Glial fibrillary acidic protein

R. glutinosa	干地黄	Geniposide	8276	T0644	Glucagon
R. glutinosa	干地黄	Cinnamic acid	3695	T0311	Glutamate--cysteine ligase catalytic subunit
R. glutinosa	干地黄	Cinnamic acid	3695	T0660	Glutathione S-transferase A2
R. glutinosa	干地黄	Geniposide	8276	T0645	Glutathione S-transferase Mu 1
R. glutinosa	干地黄	Geniposide	8276	T0646	Glutathione S-transferase Mu 2
R. glutinosa	干地黄	Cinnamic acid	3695	T0321	Glutathione S-transferase P
R. glutinosa	干地黄	Geniposide	8276	T0135	Heme oxygenase 1
R. glutinosa	干地黄	Caprylic acid	3140	T0632	Histone acetyltransferase p300
R. glutinosa	干地黄	Cinnamic acid	3695	T0441	Ig gamma-1 chain C region
R. glutinosa	干地黄	Cinnamic acid	3695	T0439	Indoleamine 2,3-dioxygenase 1
R. glutinosa	干地黄	Cinnamic acid	3695	T0003	Inhibitor of nuclear factor kappa-B kinase subunit beta
R. glutinosa	干地黄	Caprylic acid	3140	T0296	Inositol-3-phosphate synthase 1
R. glutinosa	干地黄	Nonanoic acid	15684	T0296	Inositol-3-phosphate synthase 1
R. glutinosa	干地黄	Cinnamic acid	3695	T0374	Insulin-like growth factor II
R. glutinosa	干地黄	Raffinose	18526	T0152	Intercellular adhesion molecule 1
R. glutinosa	熟地黄	Uridine	22252	T1130	Interferon alpha/beta receptor 2
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0030	Interleukin-10
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0030	Interleukin-10
R. glutinosa	干地黄	Cinnamic acid	3695	T0231	Interleukin-2
R. glutinosa	干地黄	Cinnamic acid	3695	T0276	Interleukin-4
R. glutinosa	干地黄	Cinnamic acid	3695	T0414	Interleukin-5
R. glutinosa	干地黄	Aucubin	2004	T0039	Interleukin-6
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0039	Interleukin-6
R. glutinosa	干地黄	Lauric acid	12569	T0039	Interleukin-6
R. glutinosa	干地黄	γ-Aminobutyric acid	1048	T0039	Interleukin-6

R. glutinosa	干地黄	Caprylic acid	3140	T0181	Interleukin-8
R. glutinosa	干地黄	Lauric acid	12569	T0181	Interleukin-8
R. glutinosa	干地黄	Cinnamic acid	3695	T0229	Maltase-glucoamylase, intestinal
R. glutinosa	干地黄	Cinnamic acid	3695	T0229	Maltase-glucoamylase, intestinal
R. glutinosa	干地黄	Stigmasterol	20369	T0826	Microtubule-associated protein 2
R. glutinosa	干地黄	Cinnamic acid	3695	T0029	Mitogen-activated protein kinase 1
R. glutinosa	干地黄	Raffinose	18526	T0052	Mitogen-activated protein kinase 8
R. glutinosa	干地黄	Geniposide	8276	T0204	Neuromodulin
R. glutinosa	干地黄	Aucubin	2004	T0055	NF-kappa-B inhibitor alpha
R. glutinosa	干地黄	Cinnamic acid	3695	T0206	Nitric oxide synthase, endothelial
R. glutinosa	干地黄	Catalpol	3306	T0040	Nitric oxide synthase, inducible
R. glutinosa	熟地黄	Catalpol	3306	T0040	Nitric oxide synthase, inducible
R. glutinosa	鲜地黄(生地)	Catalpol	3306	T0040	Nitric oxide synthase, inducible
R. glutinosa	干地黄	Cinnamic acid	3695	T0241	Nuclear factor of activated T-cells, cytoplasmic 3
R. glutinosa	干地黄	Caprylic acid	3140	T0360	Peroxisome proliferator-activated receptor alpha
R. glutinosa	干地黄	Myristic acid	15203	T0597	Phosphatidylcholine-sterol acyltransferase
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0286	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN
R. glutinosa	熟地黄	Uridine	22252	T1131	Phospholipase A2, membrane associated
R. glutinosa	干地黄	Geniposide	8276	T0274	Phospholipase B1, membrane-associated
R. glutinosa	干地黄	Cinnamic acid	3695	T0545	Polyphenol oxidase I, chloroplastic
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0178	Prostaglandin E2 receptor EP3 subtype
R. glutinosa	干地黄	Cinnamic acid	3695	T0179	Prostaglandin G/H synthase 1
R. glutinosa	干地黄	Cinnamic acid	3695	T0054	Prostaglandin G/H synthase 2
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0054	Prostaglandin G/H synthase 2
R. glutinosa	干地黄	Lauric acid	12569	T0054	Prostaglandin G/H synthase 2

R. glutinosa	干地黄	Stigmasterol	20369	T0077	Protein kinase C alpha type
R. glutinosa	干地黄	Cinnamic acid	3695	T0194	Protein kinase C beta type
R. glutinosa	干地黄	Cinnamic acid	3695	T1064	Prothrombin
R. glutinosa	干地黄	Cinnamic acid	3695	T0388	P-selectin
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0814	Putative beta-glucuronidase-like protein SMA3
R. glutinosa	干地黄	Lauric acid	12569	T0009	RAC-alpha serine/threonine-protein kinase
R. glutinosa	干地黄	Cinnamic acid	3695	T0752	Ras-related C3 botulinum toxin substrate 1
R. glutinosa	干地黄	Caprylic acid	3140	T0634	Retinol-binding protein 2
R. glutinosa	干地黄	Stigmasterol	20369	T0379	Serum paraoxonase/arylesterase 1
R. glutinosa	干地黄	Cinnamic acid	3695	T0092	Signal transducer and activator of transcription 1-alpha/beta
R. glutinosa	干地黄	γ-Aminobutyric acid	1048	T1228	Sodium- and chloride-dependent GABA transporter 1
R. glutinosa	干地黄	Raffinose	18526	T0862	Solute carrier family 12 member 2
R. glutinosa	干地黄	Hexadecanoic acid	9486	T1101	Solute carrier family 22 member 5
R. glutinosa	干地黄	Catalpol	3306	T0074	Superoxide dismutase [Cu-Zn]
R. glutinosa	熟地黄	Catalpol	3306	T0074	Superoxide dismutase [Cu-Zn]
R. glutinosa	鲜地黄(生地)	Catalpol	3306	T0074	Superoxide dismutase [Cu-Zn]
R. glutinosa	干地黄	Cinnamic acid	3695	T0442	T-cell surface glycoprotein CD3 zeta chain
R. glutinosa	干地黄	Cinnamic acid	3695	T0144	Tissue factor
R. glutinosa	干地黄	Cinnamic acid	3695	T0435	T-lymphocyte activation antigen CD80
R. glutinosa	干地黄	Lauric acid	12569	T0435	T-lymphocyte activation antigen CD80
R. glutinosa	干地黄	Cinnamic acid	3695	T0436	T-lymphocyte activation antigen CD86
R. glutinosa	干地黄	Lauric acid	12569	T0436	T-lymphocyte activation antigen CD86
R. glutinosa	干地黄	Cinnamic acid	3695	T0230	Trans-cinnamate 4-monooxygenase
R. glutinosa	干地黄	Stigmasterol	20369	T0038	Transcription factor AP-1
R. glutinosa	干地黄	Aucubin	2004	T0002	Transcription factor p65

R. glutinosa	干地黄	Cinnamic acid	3695	T0002	Transcription factor p65
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0002	Transcription factor p65
R. glutinosa	干地黄	Lauric acid	12569	T0002	Transcription factor p65
R. glutinosa	干地黄	Stearic acid	20280	T0129	Transcription factor Sp1
R. glutinosa	干地黄	Stigmasterol	20369	T0226	Transforming growth factor beta-1
R. glutinosa	干地黄	γ-Aminobutyric acid	1048	T0773	Transitional endoplasmic reticulum ATPase
R. glutinosa	干地黄	Aucubin	2004	T0037	Tumor necrosis factor
R. glutinosa	干地黄	Cinnamic acid	3695	T0037	Tumor necrosis factor
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0037	Tumor necrosis factor
R. glutinosa	干地黄	Hexadecanoic acid	9486	T0037	Tumor necrosis factor
R. glutinosa	干地黄	Lauric acid	12569	T0578	Tumor necrosis factor receptor superfamily member 5
R. glutinosa	干地黄	Cinnamic acid	3695	T0256	Tyrosinase
R. glutinosa	干地黄	Cinnamic acid	3695	T0326	Tyrosine-protein kinase BTK
R. glutinosa	干地黄	Cinnamic acid	3695	T0059	Xanthine dehydrogenase/oxidase
R. glutinosa	干地黄	1-Ethyl-β-D-galactoside	7440	NA	
R. glutinosa	干地黄	2'-Acetylacteoside	305	NA	
R. glutinosa	熟地黄	5-Hydroxymethyl furaldehyde	10493	NA	
R. glutinosa	干地黄	6-O-(4-Hydroxybenzoyl)-ajugol	9819	NA	
R. glutinosa	干地黄	6-O-(4"-O-α-L-Rhamnopyranosyl) vanilloylajugol	18735	NA	
R. glutinosa	干地黄	6-O-E-Feruloylajugol	7769	NA	
R. glutinosa	干地黄	6-O-p-Coumaroylajugol	4144	NA	
R. glutinosa	干地黄	6-O-Vanilloylajugol	22339	NA	
R. glutinosa	干地黄	6-O-Z-Feruloylajugol	7770	NA	
R. glutinosa	干地黄	8-Epiloganic acid	6952	NA	
R. glutinosa	干地黄	Acetylcatalpol	347	NA	

R. glutinosa	干地黄	Acteroside	580	NA	
R. glutinosa	干地黄	Adenine nucleoside	618	NA	
R. glutinosa	鲜地黄(生地)	Adenine nucleoside	618	NA	
R. glutinosa	干地黄	Ajugol	815	NA	
R. glutinosa	干地黄	Ajugoside	816	NA	
R. glutinosa	鲜地黄(生地)	Ajugoside	816	NA	
R. glutinosa	干地黄	Arachidic acid	1598	NA	
R. glutinosa	干地黄	Campesterol	3040	NA	
R. glutinosa	干地黄	Capric acid	3138	NA	
R. glutinosa	干地黄	Celebroside	3371	NA	
R. glutinosa	干地黄	cis-9,cis-12-Linoleic acid	12891	NA	
R. glutinosa	干地黄	Cistanoside A	3751	NA	
R. glutinosa	干地黄	Cistanoside F	3756	NA	
R. glutinosa	干地黄	Danmelittoside	4626	NA	
R. glutinosa	干地黄	Daturic acid	4672	NA	
R. glutinosa	干地黄	Daucosterol	4680	NA	
R. glutinosa	干地黄	Dihydrocarveol	5555	NA	
R. glutinosa	干地黄	Dihydrocatalpol	5557	NA	
R. glutinosa	干地黄	D-Mannitol	13504	NA	
R. glutinosa	干地黄	Docosanoic acid	6537	NA	
R. glutinosa	干地黄	Forsythoside A	7924	NA	
R. glutinosa	干地黄	Glucosamine	8753	NA	
R. glutinosa	干地黄	Glutinoside	8790	NA	
R. glutinosa	干地黄	Heneicosanoic acid	9360	NA	
R. glutinosa	干地黄	Isoacteoside	11195	NA	

R. glutinosa	干地黄	Jiofuran	11872	NA	
R. glutinosa	干地黄	Jioglutin A	11873	NA	
R. glutinosa	干地黄	Jioglutin B	11874	NA	
R. glutinosa	干地黄	Jioglutin C	11875	NA	
R. glutinosa	干地黄	Jioglutin D	11876	NA	
R. glutinosa	干地黄	Jioglutin E	11877	NA	
R. glutinosa	干地黄	Jioglutolide	11878	NA	
R. glutinosa	干地黄	Jioglutoside A	11879	NA	
R. glutinosa	干地黄	Jioglutoside B	11880	NA	
R. glutinosa	干地黄	Jionoside A2	11881	NA	
R. glutinosa	干地黄	Jionoside B1	11882	NA	
R. glutinosa	干地黄	Jionoside B2	11883	NA	
R. glutinosa	干地黄	Jionoside C	11884	NA	
R. glutinosa	干地黄	Jionoside D	11885	NA	
R. glutinosa	干地黄	Jionoside E	11886	NA	
R. glutinosa	鲜地黄(生地)	Manninotriose	13503	NA	
R. glutinosa	干地黄	Martynoside	13580	NA	
R. glutinosa	干地黄	Melittoside	13710	NA	
R. glutinosa	干地黄	Mioporosidegenin	14878	NA	
R. glutinosa	干地黄	Nonadecanoic acid	15672	NA	
R. glutinosa	干地黄	Palmitoleic acid	16561	NA	
R. glutinosa	干地黄	Pentadecanoic acid	16831	NA	
R. glutinosa	干地黄	Phenylacetic acid	17091	NA	
R. glutinosa	干地黄	Purpureaside A	18219	NA	
R. glutinosa	干地黄	Purpureaside B	18220	NA	

R. glutinosa	干地黄	Purpureaside C	18221	NA	
R. glutinosa	鲜地黄(生地)	Purpureaside C	18221	NA	
R. glutinosa var. purpurea	紫地黄	Purpureaside C	18221	NA	
R. glutinosa	熟地黄	Pyroglutamic acid	18266	NA	
R. glutinosa	干地黄	Rehmaglutin A	18589	NA	
R. glutinosa	熟地黄	Rehmaglutin A	18589	NA	
R. glutinosa	干地黄	Rehmaglutin B	18590	NA	
R. glutinosa	干地黄	Rehmaglutin C	18591	NA	
R. glutinosa	干地黄	Rehmaglutin D	18592	NA	
R. glutinosa	熟地黄	Rehmaglutin D	18592	NA	
R. glutinosa	干地黄	Rehmaionoside A	18593	NA	
R. glutinosa	干地黄	Rehmaionoside B	18594	NA	
R. glutinosa	干地黄	Rehmaionoside C	18595	NA	
R. glutinosa	干地黄	Rehmannioside A	18596	NA	
R. glutinosa	熟地黄	Rehmannioside A	18596	NA	
R. glutinosa	鲜地黄(生地)	Rehmannioside A	18596	NA	
R. glutinosa	干地黄	Rehmannioside B	18597	NA	
R. glutinosa	熟地黄	Rehmannioside B	18597	NA	
R. glutinosa	鲜地黄(生地)	Rehmannioside B	18597	NA	
R. glutinosa	干地黄	Rehmannioside C	18598	NA	
R. glutinosa	熟地黄	Rehmannioside C	18598	NA	
R. glutinosa	鲜地黄(生地)	Rehmannioside C	18598	NA	
R. glutinosa	干地黄	Rehmannioside D	18599	NA	
R. glutinosa	熟地黄	Rehmannioside D	18599	NA	
R. glutinosa	鲜地黄(生地)	Rehmannioside D	18599	NA	

R. glutinosa	熟地黄	Rehmapicrogenin	18600	NA	
R. glutinosa	干地黄	Rehmapicroside	18601	NA	
R. glutinosa	熟地黄	sec-Hydroxyaeginetic acid	9767	NA	
R. glutinosa	干地黄	Stachyose	20255	NA	
R. glutinosa	干地黄	Verbascose	22396	NA	
R. glutinosa	干地黄	Wiedemannioside C	22664	NA	
R. glutinosa	干地黄	β-Sitosterol	19983	NA	

Appendix 3 Biological target list for Dan shen (*Salvia miltiorrhiza, S. przewalskii var. mandarinorum, S. sinica, S. miltiorrhiza f. alba*)

Species	Chinese	Compound name	Compound ID	Target ID	Target name
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0026	72 kDa type IV collagenase
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0026	72 kDa type IV collagenase
S. miltiorrhiza	丹参	Ursolic acid	22270	T0026	72 kDa type IV collagenase
S. miltiorrhiza	丹参	Caffeic acid	2287	T0185	Acetylcholinesterase
S. miltiorrhiza	丹参	Ursolic acid	22270	T0185	Acetylcholinesterase
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0263	Actin, aortic smooth muscle
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0263	Actin, aortic smooth muscle
S. miltiorrhiza	丹参	Danshensu	4630	T1114	Actin, cytoplasmic 1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
S. sinica	拟丹参	Tanshinone IIa	20686	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
S. miltiorrhiza	丹参	Tigogenin	21383	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
S. miltiorrhiza	丹参	Hesperetic acid	9455	T0324	Alpha-1A adrenergic receptor
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0079	Amyloid beta A4 protein
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0079	Amyloid beta A4 protein
S. sinica	拟丹参	Cryptotanshinone	4292	T0079	Amyloid beta A4 protein
S. miltiorrhiza	丹参	Ursolic acid	22270	T0018	Apoptosis regulator BAX
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0013	Apoptosis regulator Bcl-2
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2

S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2
S. sinica	拟丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2
S. sinica	拟丹参	Tanshinone IIa	20686	T0013	Apoptosis regulator Bcl-2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0013	Apoptosis regulator Bcl-2
S. miltiorrhiza	丹参	Danshensu	4630	T1256	Atrial natriuretic factor
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0202	Baculoviral IAP repeat-containing protein 5
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0202	Baculoviral IAP repeat-containing protein 5
S. sinica	拟丹参	Cryptotanshinone	4292	T0202	Baculoviral IAP repeat-containing protein 5
S. miltiorrhiza	丹参	Ursolic acid	22270	T0202	Baculoviral IAP repeat-containing protein 5
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0014	Bcl-2-like protein 1
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0014	Bcl-2-like protein 1
S. sinica	拟丹参	Cryptotanshinone	4292	T0014	Bcl-2-like protein 1
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0014	Bcl-2-like protein 1
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0014	Bcl-2-like protein 1
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0014	Bcl-2-like protein 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0014	Bcl-2-like protein 1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0238	Calcitonin receptor
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0238	Calcitonin receptor
S. sinica	拟丹参	Tanshinone IIa	20686	T0238	Calcitonin receptor
S. miltiorrhiza	丹参	Ursolic acid	22270	T0213	Caspase-1
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0045	Caspase-3

S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0045	Caspase-3
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0045	Caspase-3
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0045	Caspase-3
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0045	Caspase-3
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0045	Caspase-3
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0045	Caspase-3
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0045	Caspase-3
S. sinica	拟丹参	Tanshinone IIa	20686	T0045	Caspase-3
S. miltiorrhiza	丹参	Ursolic acid	22270	T0045	Caspase-3
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0143	Caspase-7
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0143	Caspase-7
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0143	Caspase-7
S. miltiorrhiza	丹参	Ursolic acid	22270	T0060	Caspase-8
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0019	Caspase-9
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0019	Caspase-9
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0019	Caspase-9
S. miltiorrhiza	丹参	Ursolic acid	22270	T0019	Caspase-9
S. miltiorrhiza	丹参	Ursolic acid	22270	T0207	Cathepsin B
S. miltiorrhiza	丹参	Ferruginol	7764	T1248	CD83 antigen
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0034	Cell division protein kinase 2
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0034	Cell division protein kinase 2
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0034	Cell division protein kinase 2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0034	Cell division protein kinase 2

S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0035	Cell division protein kinase 4
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0035	Cell division protein kinase 4
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0035	Cell division protein kinase 4
S. miltiorrhiza	丹参	Ursolic acid	22270	T0035	Cell division protein kinase 4
S. miltiorrhiza	丹参	Ursolic acid	22270	T0041	Cell division protein kinase 6
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0046	Cellular tumor antigen p53
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0046	Cellular tumor antigen p53
S. sinica	拟丹参	Tanshinone IIa	20686	T0046	Cellular tumor antigen p53
S. miltiorrhiza	丹参	Ursolic acid	22270	T0046	Cellular tumor antigen p53
S. miltiorrhiza	丹参	Ursolic acid	22270	T0200	C-Jun-amino-terminal kinase-interacting protein 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0201	C-Jun-amino-terminal kinase-interacting protein 2
S. miltiorrhiza	丹参	Danshensu	4630	T0267	Collagen alpha-1(I) chain
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0267	Collagen alpha-1(I) chain
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0267	Collagen alpha-1(I) chain
S. miltiorrhiza	丹参	Danshensu	4630	T0344	Collagen alpha-1(III) chain
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0225	Collagen alpha-1(VII) chain
S. miltiorrhiza	丹参	Ursolic acid	22270	T0196	Cyclic AMP-dependent transcription factor ATF-2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0157	Cyclic AMP-responsive element-binding protein 1
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0016	Cyclin-dependent kinase inhibitor 1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0016	Cyclin-dependent kinase inhibitor 1

S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0016	Cyclin-dependent kinase inhibitor 1
S. sinica	拟丹参	Tanshinone IIa	20686	T0016	Cyclin-dependent kinase inhibitor 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0016	Cyclin-dependent kinase inhibitor 1
S. miltiorrhiza	丹参	Caffeic acid	2287	T0150	Cytochrome P450 1A1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0150	Cytochrome P450 1A1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0150	Cytochrome P450 1A1
S. sinica	拟丹参	Tanshinone IIa	20686	T0150	Cytochrome P450 1A1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0138	Cytochrome P450 1A2
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0138	Cytochrome P450 1A2
S. sinica	拟丹参	Tanshinone IIa	20686	T0138	Cytochrome P450 1A2
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0136	Cytochrome P450 3A4
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0136	Cytochrome P450 3A4
S. sinica	拟丹参	Tanshinone IIa	20686	T0136	Cytochrome P450 3A4
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0205	Dual oxidase 2
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0205	Dual oxidase 2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0205	Dual oxidase 2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0310	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0106	Endothelin-1
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0106	Endothelin-1
S. sinica	拟丹参	Cryptotanshinone	4292	T0106	Endothelin-1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0106	Endothelin-1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0106	Endothelin-1

S. sinica	拟丹参	Tanshinone IIa	20686	T0106	Endothelin-1
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0105	Endothelin-1 receptor
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0105	Endothelin-1 receptor
S. sinica	拟丹参	Tanshinone IIa	20686	T0105	Endothelin-1 receptor
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0236	Endothelin-converting enzyme 1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0236	Endothelin-converting enzyme 1
S. sinica	拟丹参	Tanshinone IIa	20686	T0236	Endothelin-converting enzyme 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0174	E-selectin
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0017	Eukaryotic translation initiation factor 6
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0017	Eukaryotic translation initiation factor 6
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0017	Eukaryotic translation initiation factor 6
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0017	Eukaryotic translation initiation factor 6
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0061	Fatty acid synthase
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0061	Fatty acid synthase
S. sinica	拟丹参	Tanshinone IIa	20686	T0061	Fatty acid synthase
S. miltiorrhiza	丹参	Ursolic acid	22270	T0061	Fatty acid synthase
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0012	G1/S-specific cyclin-D1
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0012	G1/S-specific cyclin-D1
S. sinica	拟丹参	Cryptotanshinone	4292	T0012	G1/S-specific cyclin-D1
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0012	G1/S-specific cyclin-D1
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0012	G1/S-specific cyclin-D1
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0012	G1/S-specific cyclin-D1
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0012	G1/S-specific cyclin-D1

S. miltiorrhiza	丹参	Ursolic acid	22270	T0012	G1/S-specific cyclin-D1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0211	G1/S-specific cyclin-D2
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0246	G1/S-specific cyclin-D3
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0246	G1/S-specific cyclin-D3
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0246	G1/S-specific cyclin-D3
S. miltiorrhiza	丹参	Caffeic acid	2287	T0346	Glial fibrillary acidic protein
S. miltiorrhiza	丹参	Ursolic acid	22270	T0197	Granulocyte-macrophage colony-stimulating factor
S. miltiorrhiza	丹参	Ursolic acid	22270	T0116	Heparin-binding growth factor 2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0182	Induced myeloid leukemia cell differentiation protein Mcl-1
S. miltiorrhiza	丹参	Caffeic acid	2287	T0374	Insulin-like growth factor II
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0239	Integrin beta-3
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0239	Integrin beta-3
S. sinica	拟丹参	Tanshinone IIa	20686	T0239	Integrin beta-3
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0152	Intercellular adhesion molecule 1
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0152	Intercellular adhesion molecule 1
S. miltiorrhiza	丹参	Tanshinone I	20685	T0152	Intercellular adhesion molecule 1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone I	20685	T0152	Intercellular adhesion molecule 1
S. sinica	拟丹参	Tanshinone I	20685	T0152	Intercellular adhesion molecule 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0152	Intercellular adhesion molecule 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0156	Interleukin-1 beta
S. miltiorrhiza	丹参	Ursolic acid	22270	T0039	Interleukin-6
S. miltiorrhiza	丹参	Ursolic acid	22270	T0086	Interstitial collagenase
S. miltiorrhiza	丹参	Ursolic acid	22270	T0210	Lipopolysaccharide-induced tumor necrosis factor-alpha factor

S. sinica	拟丹参	3,4-Dihydroxybenzoic acid	5763	T0229	Maltase-glucoamylase, intestinal
S. miltiorrhiza	丹参	3,8-Dihydroxybenzoic acid	5763	T0229	Maltase-glucoamylase, intestinal
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0027	Matrix metalloproteinase-9
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0027	Matrix metalloproteinase-9
S. sinica	拟丹参	Tanshinone IIa	20686	T0027	Matrix metalloproteinase-9
S. miltiorrhiza	丹参	Ursolic acid	22270	T0027	Matrix metalloproteinase-9
S. miltiorrhiza	丹参	Danshensu	4630	T0082	Metalloproteinase inhibitor 1
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0029	Mitogen-activated protein kinase 1
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0029	Mitogen-activated protein kinase 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0052	Mitogen-activated protein kinase 8
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. miltiorrhiza	拟丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. miltiorrhiza	拟丹参	Tanshinone IIa	20686	T0142	Myc proto-oncogene protein
S. miltiorrhiza	丹参	Danshensu	4630	T1257	Neurofibromin
S. miltiorrhiza	丹参	Ursolic acid	22270	T0204	Neuromodulin
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0055	NF-kappa-B inhibitor alpha
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0055	NF-kappa-B inhibitor alpha
S. sinica	拟丹参	Tanshinone IIa	20686	T0055	NF-kappa-B inhibitor alpha
S. miltiorrhiza	丹参	Ursolic acid	22270	T0055	NF-kappa-B inhibitor alpha
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0206	Nitric oxide synthase, endothelial
S. przewalskii var.	紫丹参	Tanshinone IIa	20686	T0206	Nitric oxide synthase, endothelial

mandarinorum					
S. sinica	拟丹参	Tanshinone IIa	20686	T0206	Nitric oxide synthase, endothelial
S. miltiorrhiza	丹参	Ursolic acid	22270	T0206	Nitric oxide synthase, endothelial
S. miltiorrhiza	丹参	Ursolic acid	22270	T0040	Nitric oxide synthase, inducible
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0234	Nuclear receptor subfamily 1 group I member 2
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0234	Nuclear receptor subfamily 1 group I member 2
S. sinica	拟丹参	Tanshinone IIa	20686	T0234	Nuclear receptor subfamily 1 group I member 2
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0235	Nucleophosmin
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0235	Nucleophosmin
S. sinica	拟丹参	Tanshinone IIa	20686	T0235	Nucleophosmin
S. miltiorrhiza	丹参	Protocatechuic aldehyde	17968	T0058	Ornithine decarboxylase
S. przewalskii var. mandarinorum	紫丹参	Protocatechuic aldehyde	17968	T0058	Ornithine decarboxylase
S. sinica	拟丹参	Protocatechuic aldehyde	17968	T0058	Ornithine decarboxylase
S. miltiorrhiza	丹参	Ursolic acid	22270	T0209	Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0265	Plasminogen activator inhibitor 1
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0265	Plasminogen activator inhibitor 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0198	Platelet endothelial cell adhesion molecule
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0237	Poly [ADP-ribose] polymerase 4
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0237	Poly [ADP-ribose] polymerase 4
S. sinica	拟丹参	Tanshinone IIa	20686	T0237	Poly [ADP-ribose] polymerase 4
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0266	PRKC apoptosis WT1 regulator protein

S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0266	PRKC apoptosis WT1 regulator protein
S. miltiorrhiza	丹参	Dihydrotanshinone I	5722	T0099	Probable E3 ubiquitin-protein ligase HERC5
S. przewalskii var. mandarinorum	紫丹参	Dihydrotanshinone I	5722	T0099	Probable E3 ubiquitin-protein ligase HERC5
S. sinica	拟丹参	Dihydrotanshinone I	5722	T0099	Probable E3 ubiquitin-protein ligase HERC5
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0099	Probable E3 ubiquitin-protein ligase HERC5
S. miltiorrhiza	丹参	Ursolic acid	22270	T0099	Probable E3 ubiquitin-protein ligase HERC5
S. miltiorrhiza	丹参	Ursolic acid	22270	T0178	Prostaglandin E2 receptor EP3 subtype
S. miltiorrhiza	丹参	Caffeic acid	2287	T0179	Prostaglandin G/H synthase 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0179	Prostaglandin G/H synthase 1
S. miltiorrhiza	丹参	Caffeic acid	2287	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	Tigogenin	21383	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	Tigogenin	21383	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	Ursolic acid	22270	T0054	Prostaglandin G/H synthase 2
S. miltiorrhiza	丹参	3,4-Dihydroxybenzoic acid	5763	T0077	Protein kinase C alpha type
S. sinica	拟丹参	3,4-Dihydroxybenzoic acid	5763	T0077	Protein kinase C alpha type
S. sinica	拟丹参	3,4-Dihydroxybenzoic acid	5763	T0194	Protein kinase C beta type
S. miltiorrhiza	丹参	3,5-Dihydroxybenzoic acid	5763	T0194	Protein kinase C beta type
S. miltiorrhiza	丹参	Caffeic acid	2287	T0194	Protein kinase C beta type
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0194	Protein kinase C beta type
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0194	Protein kinase C beta type
S. sinica	拟丹参	3,4-Dihydroxybenzoic acid	5763	T0195	Protein kinase C gamma type
S. miltiorrhiza	丹参	3,6-Dihydroxybenzoic acid	5763	T0195	Protein kinase C gamma type
S. miltiorrhiza	丹参	Ursolic acid	22270	T0195	Protein kinase C gamma type

S. sinica	拟丹参	3,4-Dihydroxybenzoic acid	5763	T1277	Protein kinase C zeta type
S. miltiorrhiza	丹参	3,7-Dihydroxybenzoic acid	5763	T1277	Protein kinase C zeta type
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0015	Proto-oncogene c-Fos
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0015	Proto-oncogene c-Fos
S. sinica	拟丹参	Tanshinone IIa	20686	T0015	Proto-oncogene c-Fos
S. miltiorrhiza	丹参	Ursolic acid	22270	T0015	Proto-oncogene c-Fos
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0199	Proto-oncogene tyrosine-protein kinase Src
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0199	Proto-oncogene tyrosine-protein kinase Src
S. sinica	拟丹参	Tanshinone IIa	20686	T0199	Proto-oncogene tyrosine-protein kinase Src
S. miltiorrhiza	丹参	Ursolic acid	22270	T0199	Proto-oncogene tyrosine-protein kinase Src
S. miltiorrhiza	丹参	Caffeic acid	2287	T0388	P-selectin
S. miltiorrhiza	丹参	Salvianolic acid A	19201	T0009	RAC-alpha serine/threonine-protein kinase
S. miltiorrhiza	丹参	Caffeic acid	2287	T0752	Ras-related C3 botulinum toxin substrate 1
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0260	Ryanodine receptor 2
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0260	Ryanodine receptor 2
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0008	Signal transducer and activator of transcription 3
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0008	Signal transducer and activator of transcription 3
S. sinica	拟丹参	Cryptotanshinone	4292	T0008	Signal transducer and activator of transcription 3
S. miltiorrhiza	丹参	Ursolic acid	22270	T0008	Signal transducer and activator of transcription 3
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0264	Spermatogenic leucine zipper protein 1

S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0264	Spermatogenic leucine zipper protein 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0087	Stromelysin-1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0146	Stromelysin-2
S. miltiorrhiza	丹参	Danshensu	4630	T0074	Superoxide dismutase [Cu-Zn]
S. miltiorrhiza	丹参	Ferruginol	7764	T0577	T-cell surface glycoprotein CD1a
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0262	Thrombomodulin
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0262	Thrombomodulin
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0261	Tissue-type plasminogen activator
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0261	Tissue-type plasminogen activator
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0038	Transcription factor AP-1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0038	Transcription factor AP-1
S. sinica	拟丹参	Tanshinone IIa	20686	T0038	Transcription factor AP-1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0038	Transcription factor AP-1
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0002	Transcription factor p65
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0002	Transcription factor p65
S. sinica	拟丹参	Cryptotanshinone	4292	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Danshensu	4630	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Tanshinone IIa	20686	T0002	Transcription factor p65
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIa	20686	T0002	Transcription factor p65
S. sinica	拟丹参	Tanshinone IIa	20686	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Ursolic acid	22270	T0002	Transcription factor p65
S. miltiorrhiza	丹参	Danshensu	4630	T0226	Transforming growth factor beta-1

S. miltiorrhiza	丹参	Caffeic acid	2287	T0037	Tumor necrosis factor
S. miltiorrhiza	丹参	Cryptotanshinone	4292	T0037	Tumor necrosis factor
S. przewalskii var. mandarinorum	紫丹参	Cryptotanshinone	4292	T0037	Tumor necrosis factor
S. sinica	拟丹参	Cryptotanshinone	4292	T0037	Tumor necrosis factor
S. miltiorrhiza	丹参	Ursolic acid	22270	T0037	Tumor necrosis factor
S. miltiorrhiza	丹参	Ursolic acid	22270	T0212	Tumor necrosis factor ligand superfamily member 6
S. miltiorrhiza	丹参	Caffeic acid	2287	T0326	Tyrosine-protein kinase BTK
S. miltiorrhiza	丹参	Ursolic acid	22270	T0208	Tyrosine-protein phosphatase non-receptor type 1
S. miltiorrhiza	丹参	Ursolic acid	22270	T0203	Tyrosine-protein phosphatase non-receptor type 6
S. miltiorrhiza	丹参	Ursolic acid	22270	T0025	Urokinase-type plasminogen activator
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0175	Vascular cell adhesion protein 1
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0175	Vascular cell adhesion protein 1
S. miltiorrhiza	丹参	Tanshinone I	20685	T0175	Vascular cell adhesion protein 1
S. przewalskii var. mandarinorum	紫丹参	Tanshinone I	20685	T0175	Vascular cell adhesion protein 1
S. sinica	拟丹参	Tanshinone I	20685	T0175	Vascular cell adhesion protein 1
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0010	Vascular endothelial growth factor A
S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0010	Vascular endothelial growth factor A
S. miltiorrhiza	丹参	Tanshinone I	20685	T0010	Vascular endothelial growth factor A
S. przewalskii var. mandarinorum	紫丹参	Tanshinone I	20685	T0010	Vascular endothelial growth factor A
S. sinica	拟丹参	Tanshinone I	20685	T0010	Vascular endothelial growth factor A
S. miltiorrhiza	丹参	Ursolic acid	22270	T0010	Vascular endothelial growth factor A
S. miltiorrhiza	丹参	Lithospermic acid B	12926	T0021	Vascular endothelial growth factor receptor 2

S. miltiorrhiza	丹参	Salvianolic Acid B	19202	T0021	Vascular endothelial growth factor receptor 2
S. miltiorrhiza f. alba	白花丹参	1,2,15,16-Tetrahydrotanshinone I	21080	NA	
S. miltiorrhiza	丹参	1,2-Dihydrotanshiquinone	5723	NA	
S. miltiorrhiza	丹参	1-Keto-isocryptotanshinone	12204	NA	
S. miltiorrhiza	丹参	2-Isopropyl-8-methylphenanthrene-3,4-dione(R0-090680)	11629	NA	
S. miltiorrhiza	丹参	3α-Hydroxytanshinone IIA	10736	NA	
S. miltiorrhiza	丹参	3-β-Hydroxymethylenetanshiquinone	10492	NA	
S. miltiorrhiza	丹参	3β-Hydroxytanshinone IIA	10737	NA	
S. miltiorrhiza	丹参	Baicalin	2106	NA	
S. miltiorrhiza	丹参	Danshenol A	4627	NA	
S. miltiorrhiza	丹参	Danshenol B	4628	NA	
S. miltiorrhiza	丹参	Danshenspiroketallactone	4629	NA	
S. miltiorrhiza	丹参	Danshensuan B	4631	NA	
S. miltiorrhiza	丹参	Danshenxinkun A	4632	NA	
S. miltiorrhiza	丹参	Danshenxinkun B	4633	NA	
S. miltiorrhiza	丹参	Danshenxinkun C	4634	NA	
S. miltiorrhiza	丹参	Danshenxinkun D	4635	NA	
S. miltiorrhiza	丹参	Daucosterol	4680	NA	
S. miltiorrhiza	丹参	Dehydromiltirone	4950	NA	
S. miltiorrhiza	丹参	Dihydroisotanshinone I	5653	NA	
S. miltiorrhiza	丹参	Epidanshenspiroketallactone	6877	NA	
S. miltiorrhiza	丹参	Isocryptotanshinone	11354	NA	
S. miltiorrhiza	丹参	Isotanshinone I	11729	NA	
S. miltiorrhiza	丹参	Isotanshinone IIA	11731	NA	
S. miltiorrhiza	丹参	Labiatenic acid	12420	NA	

S. miltiorrhiza	丹参	Lithospermate B	12924	NA	
S. miltiorrhiza	丹参	Magnesium lithospermate B	13370	NA	
S. miltiorrhiza	丹参	Methyl tanshinonate	14736	NA	
S. przewalskii var. mandarinorum	紫丹参	Methyl tanshinonate	14736	NA	
S. sinica	拟丹参	Methyl tanshinonate	14736	NA	
S. miltiorrhiza	丹参	Methylene tanshinquinone	14391	NA	
S. przewalskii var. mandarinorum	紫丹参	Methylene tanshinquinone	14391	NA	
S. sinica	拟丹参	Methylene tanshinquinone	14391	NA	
S. miltiorrhiza	丹参	Miltionone I	14862	NA	
S. miltiorrhiza	丹参	Miltionone II	14863	NA	
S. miltiorrhiza	丹参	Miltipolone	14864	NA	
S. miltiorrhiza	丹参	Miltirone	14865	NA	
S. miltiorrhiza	丹参	Monomethyl lithospermate	14927	NA	
S. miltiorrhiza	丹参	Neocryptotanshinone	15374	NA	
S. miltiorrhiza	丹参	Neocryptotanshinone II	15375	NA	
S. miltiorrhiza	丹参	Nortanshinone	15801	NA	
S. miltiorrhiza	丹参	Oleoyl danshenxinkun A	16072	NA	
S. miltiorrhiza	丹参	Oleoyl neocryptotanshinone	16073	NA	
S. przewalskii var. mandarinorum	紫丹参	Przewaquinone A	18011	NA	
S. miltiorrhiza	丹参	Przewaquinone B	18012	NA	
S. przewalskii var. mandarinorum	紫丹参	Przewaquinone B	18012	NA	
S. sinica	拟丹参	Przewaquinone B	18012	NA	
S. przewalskii var. mandarinorum	紫丹参	Przewaquinone F	18013	NA	

S. miltiorrhiza	丹参	Rosmarinic acid methyl ester	18925	NA	
S. miltiorrhiza	丹参	Salvianolic acid C	19203	NA	
S. miltiorrhiza	丹参	Salvianolic acid D	19204	NA	
S. miltiorrhiza	丹参	Salvianolic acid E	19205	NA	
S. miltiorrhiza	丹参	Salvianolic acid G	19207	NA	
S. miltiorrhiza	丹参	Salvilenone	19217	NA	
S. miltiorrhiza	丹参	Salvinone	19218	NA	
S. miltiorrhiza	丹参	Salviol	19219	NA	
S. miltiorrhiza f. alba	白花丹参	Tanshinaldehyde	20678	NA	
S. miltiorrhiza	丹参	Tanshindiol A	20679	NA	
S. miltiorrhiza	丹参	Tanshindiol B	20680	NA	
S. miltiorrhiza	丹参	Tanshindiol C	20681	NA	
S. miltiorrhiza	丹参	Tanshinlactone	20682	NA	
S. miltiorrhiza	丹参	Tanshinol A	20683	NA	
S. miltiorrhiza	丹参	Tanshinol B	20684	NA	
S. miltiorrhiza	丹参	Tanshinone IIb	20687	NA	
S. przewalskii var. mandarinorum	紫丹参	Tanshinone IIb	20687	NA	
S. sinica	拟丹参	Tanshinone IIb	20687	NA	
S. miltiorrhiza	丹参	Tanshinone VI	20688	NA	
S. miltiorrhiza	丹参	β-Sitosterol	19983	NA	
S. miltiorrhiza	丹参	Δ1-Dehydrotanshinone	4974	NA	

Appendix 4 Biological target list for Lu hui (*Aloe vera, A. vera var. chinensis, A. ferox, A. spp.*)

Species	Chinese	Compound name	Compound ID	Target ID	Target name
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0291	3-hydroxy-3-methylglutaryl-coenzyme A reductase
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T1114	Actin, cytoplasmic 1
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0510	Aldose reductase
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1162	Alpha-amylase 1
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0013	Apoptosis regulator Bcl-2
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0279	Arachidonate 5-lipoxygenase
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T1116	BMP-binding endothelial regulator protein
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0476	C5a anaphylatoxin chemotactic receptor
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0318	Calmodulin
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0045	Caspase-3
A. vera	芦荟(库拉索芦荟)	Succinic acid	20444	T0045	Caspase-3
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0075	Catalase
A. vera	芦荟(库拉索芦荟)	p-Coumaric acid	4135	T0546	C-C motif chemokine 16
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1163	Chitinase-3-like protein 1
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T1102	Choline-phosphate cytidylyltransferase A
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0267	Collagen alpha-1(I) chain
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0267	Collagen alpha-1(I) chain
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0225	Collagen alpha-1(VII) chain
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0138	Cytochrome P450 1A2
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0554	Delta-aminolevulinic acid dehydratase
A. vera var.	斑纹芦荟	Lauric acid	12569	T0205	Dual oxidase 2

chinensis					
A. vera var. chinensis	斑纹芦荟	Stearic acid	20280	T0310	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0061	Fatty acid synthase
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0094	Fos-related antigen 2
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0675	Glucose-6-phosphatase
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0485	Glutamine synthetase
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0321	Glutathione S-transferase P
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T1002	Hepatocyte nuclear factor 1-alpha
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0775	Hepatocyte nuclear factor 4-alpha
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1164	Hexokinase-1
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0316	Hyaluronan synthase 2
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0506	Insulin
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T1153	Integrin beta-2
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0156	Interleukin-1 beta
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0030	Interleukin-10
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0030	Interleukin-10
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0039	Interleukin-6
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0039	Interleukin-6
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0039	Interleukin-6
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0181	Interleukin-8
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0181	Interleukin-8
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0594	Lactase-phlorizin hydrolase

A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1165	Long-chain-fatty-acid--CoA ligase 1
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1166	Long-chain-fatty-acid--CoA ligase 4
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0617	Low affinity immunoglobulin epsilon Fc receptor
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0846	Mitochondrial uncoupling protein 2
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0142	Myc proto-oncogene protein
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0057	NADPH--cytochrome P450 reductase
A. vera	芦荟(库拉索芦荟)	p-Coumaric acid	4135	T0206	Nitric oxide synthase, endothelial
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0040	Nitric oxide synthase, inducible
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0356	Nuclear receptor subfamily 1 group I member 3
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T1106	Pancreatic alpha-amylase
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0125	Peroxisome proliferator-activated receptor gamma
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0286	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN
A. vera	芦荟(库拉索芦荟)	p-Coumaric acid	4135	T0545	Polyphenol oxidase I, chloroplastic
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0101	Proliferating cell nuclear antigen
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0178	Prostaglandin E2 receptor EP3 subtype
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0054	Prostaglandin G/H synthase 2
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0054	Prostaglandin G/H synthase 2
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0054	Prostaglandin G/H synthase 2
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0194	Protein kinase C beta type
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0015	Proto-oncogene c-Fos
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0814	Putative beta-glucuronidase-like protein SMA3
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0009	RAC-alpha serine/threonine-protein kinase
A. vera var.	斑纹芦荟	Linolenic acid	12893	T0139	Serum albumin

chinensis					
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T1101	Solute carrier family 22 member 5
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0465	Sterol regulatory element-binding protein 1
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0132	Sterol regulatory element-binding protein 2
A. vera	芦荟(库拉索芦荟)	Sucrose	20446	T0593	Sucrase-isomaltase, intestinal
A. vera	芦荟(库拉索芦荟)	Glucuronic acid	8761	T0074	Superoxide dismutase [Cu-Zn]
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0074	Superoxide dismutase [Cu-Zn]
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T1246	Thromboxane A2 receptor
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0435	T-lymphocyte activation antigen CD80
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0436	T-lymphocyte activation antigen CD86
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0002	Transcription factor p65
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0002	Transcription factor p65
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T0002	Transcription factor p65
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0002	Transcription factor p65
A. vera var. chinensis	斑纹芦荟	Stearic acid	20280	T0129	Transcription factor Sp1
A. vera var. chinensis	斑纹芦荟	Linolenic acid	12893	T1115	Tripartite motif-containing protein 26
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0037	Tumor necrosis factor
A. vera	芦荟(库拉索芦荟)	Hexadecanoic acid	9486	T0037	Tumor necrosis factor
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0037	Tumor necrosis factor
A. vera var. chinensis	斑纹芦荟	Lauric acid	12569	T0578	Tumor necrosis factor receptor superfamily member 5
A. vera	芦荟(库拉索芦荟)	Rutin	19087	T0380	Type I iodothyronine deiodinase
A. vera	芦荟(库拉索芦荟)	p-Coumaric acid	4135	T0256	Tyrosinase
A. vera	芦荟(库拉索芦荟)	2"-O-Feruloylaloesin	7772	NA	

A. vera	芦荟(库拉索芦荟)	6'-O-p-Coumaroylaloesin	4146	NA	
A. vera	芦荟(库拉索芦荟)	7-Hydroxyaloin A	9773	NA	
A. ferox	好望角芦荟	Aloeemodin	967	NA	
A. vera	芦荟(库拉索芦荟)	Aloeemodin	967	NA	
A. vera var. chinensis	斑纹芦荟	Aloeemodin	967	NA	
A. vera	芦荟(库拉索芦荟)	Aloenin	972	NA	
A. spp.	多种芦荟提取物	Aloeresin A	973	NA	
A. vera	芦荟(库拉索芦荟)	Aloeresin A	973	NA	
A. ferox	好望角芦荟	Aloeresin C	974	NA	
A. ferox	好望角芦荟	Aloeresin D	975	NA	
A. vera	芦荟(库拉索芦荟)	Aloeresin G	976	NA	
A. ferox	好望角芦荟	Aloeresin H	977	NA	
A. ferox	好望角芦荟	Aloeresin I	978	NA	
A. vera var. chinensis	斑纹芦荟	Aloesin	979	NA	
A. ferox	好望角芦荟	Aloesone	980	NA	
A. ferox	好望角芦荟	Aloin	981	NA	
A. vera	芦荟(库拉索芦荟)	Aloin	981	NA	
A. vera var. chinensis	斑纹芦荟	Aloin	981	NA	
A. vera	芦荟(库拉索芦荟)	Anthranol	1365	NA	
A. vera	芦荟(库拉索芦荟)	Campesterol	3040	NA	
A. vera	芦荟(库拉索芦荟)	Campherenol	3046	NA	
A. vera	芦荟(库拉索芦荟)	Capric acid	3138	NA	
A. vera	芦荟(库拉索芦荟)	Cholesterol	3585	NA	
A. vera	芦荟(库拉索芦荟)	Chrysophanol	3615	NA	

A. vera var. chinensis	斑纹芦荟	cis-9,cis-12-Linoleic acid	12891	NA	
A. vera	芦荟(库拉索芦荟)	Daturic acid	4672	NA	
A. ferox	好望角芦荟	Feralolide	7755	NA	
A. ferox	好望角芦荟	Feroxidin	7761	NA	
A. ferox	好望角芦荟	Feroxin A	7762	NA	
A. ferox	好望角芦荟	Feroxin B	7763	NA	
A. vera	芦荟(库拉索芦荟)	Helminthosporin	9333	NA	
A. vera	芦荟(库拉索芦荟)	Homonataloin	9615	NA	
A. ferox	好望角芦荟	Isoaloeresin A	11204	NA	
A. vera	芦荟(库拉索芦荟)	Isoaloesin	11205	NA	
A. vera	芦荟(库拉索芦荟)	Isoeleutherol glucoside	11409	NA	
A. vera	芦荟(库拉索芦荟)	Lactic acid	12436	NA	
A. vera	芦荟(库拉索芦荟)	Magnesium lactate	13368	NA	
A. vera	芦荟(库拉索芦荟)	Mannose	13507	NA	
A. vera	芦荟(库拉索芦荟)	Mannose-b	13508	NA	
A. vera var. chinensis	斑纹芦荟	Palmitoleic acid	16561	NA	
A. vera	芦荟(库拉索芦荟)	Pentadecanoic acid	16381	NA	
A. vera	芦荟(库拉索芦荟)	Rhamnose	18739	NA	
A. vera	芦荟(库拉索芦荟)	Xylose	20843	NA	
A. vera var. chinensis	斑纹芦荟	β-Carotene	3209	NA	

Appendix 5 Biological target list for Qing dai (*Indigo naturalis* sourced from *Isatis indigotica, I. tinctoria, B. cusia, S. formosanus*)

Species	**Chinese**	**Compound**	**Compound ID**	**Target ID**	**Target name**
B. cusia	马蓝根	Lupeol	13098	T0628	14-3-3 protein sigma
I. indigotica	板蓝根	Salicylic acid	19187	T0831	6-phosphofructokinase, muscle type
I. indigotica	板蓝根	Salicylic acid	19187	T0881	Aldo-keto reductase family 1 member C1
I. indigotica	大青叶	Sucrose	20446	T0510	Aldose reductase
I. indigotica	大青叶	Sucrose	20446	T1162	Alpha-amylase 1
I. indigotica	板蓝根	Salicylic acid	19187	T0517	Apolipoprotein A-I
B. cusia	马蓝根	Lupeol	13098	T0018	Apoptosis regulator BAX
I. indigotica	板蓝根	β-Sitosterol	19983	T0018	Apoptosis regulator BAX
I. indigotica	大青叶	β-Sitosterol	19983	T0018	Apoptosis regulator BAX
I. indigotica	大青叶	Hexadecanoic acid	9486	T0013	Apoptosis regulator Bcl-2
B. cusia	马蓝根	Lupeol	13098	T0013	Apoptosis regulator Bcl-2
I. indigotica	板蓝根	β-Sitosterol	19983	T0013	Apoptosis regulator Bcl-2
I. indigotica	大青叶	β-Sitosterol	19983	T0013	Apoptosis regulator Bcl-2
B. cusia	马蓝根	Lupeol	13098	T0463	Apoptotic protease-activating factor 1
I. indigotica	板蓝根	Salicylic acid	19187	T0279	Arachidonate 5-lipoxygenase
B. cusia	马蓝根	Indirubin	11024	T0332	Aryl hydrocarbon receptor
I. indigotica	板蓝根	Indirubin	11024	T0332	Aryl hydrocarbon receptor
I. indigotica	大青叶	Indirubin	11024	T0332	Aryl hydrocarbon receptor
*S. formosanus**	台湾马蓝*	Indirubin	11024	T0332	Aryl hydrocarbon receptor
I. indigotica	板蓝根	Salicylic acid	19187	T1062	Beta-glucuronidase

B. cusia	马蓝根	Lupeol	13098	T0629	Carnitine O-acetyltransferase
B. cusia	马蓝根	Lupeol	13098	T0045	Caspase-3
B. cusia	马蓝根	Tryptanthrine	22059	T0045	Caspase-3
I. indigotica	板蓝根	Tryptanthrine	22059	T0045	Caspase-3
I. indigotica	大青叶	Tryptanthrine	22059	T0045	Caspase-3
I. tinctoria	欧州菘蓝	Tryptanthrine	22059	T0045	Caspase-3
I. indigotica	板蓝根	β-Sitosterol	19983	T0045	Caspase-3
I. indigotica	大青叶	β-Sitosterol	19983	T0045	Caspase-3
I. indigotica	板蓝根	β-Sitosterol	19983	T0060	Caspase-8
I. indigotica	大青叶	β-Sitosterol	19983	T0060	Caspase-8
B. cusia	马蓝根	Lupeol	13098	T0019	Caspase-9
I. indigotica	板蓝根	β-Sitosterol	19983	T0019	Caspase-9
I. indigotica	大青叶	β-Sitosterol	19983	T0019	Caspase-9
I. indigotica	板蓝根	Salicylic acid	19187	T0075	Catalase
B. cusia	马蓝根	Indirubin	11024	T0447	C-C motif chemokine 5
I. indigotica	板蓝根	Indirubin	11024	T0447	C-C motif chemokine 5
I. indigotica	大青叶	Indirubin	11024	T0447	C-C motif chemokine 5
S. formosanus	台湾马蓝	Indirubin	11024	T0447	C-C motif chemokine 5
B. cusia	马蓝根	Lupeol	13098	T0100	Cell division control protein 2 homolog
I. indigotica	大青叶	Sucrose	20446	T1163	Chitinase-3-like protein 1
I. indigotica	大青叶	Hexadecanoic acid	9486	T1102	Choline-phosphate cytidylyltransferase A
I. indigotica	大青叶	Hexadecanoic acid	9486	T0267	Collagen alpha-1(I) chain
I. indigotica	大青叶	Sucrose	20446	T0267	Collagen alpha-1(I) chain

I. indigotica	大青叶	Sucrose	20446	T0225	Collagen alpha-1(VII) chain
B. cusia	马蓝根	Indirubin	11024	T0583	Cyclin-dependent kinase inhibitor 3
I. indigotica	板蓝根	Indirubin	11024	T0583	Cyclin-dependent kinase inhibitor 3
I. indigotica	大青叶	Indirubin	11024	T0583	Cyclin-dependent kinase inhibitor 3
S. formosanus	台湾马蓝	Indirubin	11024	T0583	Cyclin-dependent kinase inhibitor 3
B. cusia	马蓝根	Indirubin	11024	T0150	Cytochrome P450 1A1
I. indigotica	板蓝根	Indirubin	11024	T0150	Cytochrome P450 1A1
I. indigotica	大青叶	Indirubin	11024	T0150	Cytochrome P450 1A1
S. formosanus	台湾马蓝	Indirubin	11024	T0150	Cytochrome P450 1A1
I. indigotica	大青叶	Sucrose	20446	T0138	Cytochrome P450 1A2
I. indigotica	大青叶	Sucrose	20446	T0554	Delta-aminolevulinic acid dehydratase
I. indigotica	板蓝根	Salicylic acid	19187	T0106	Endothelin-1
B. cusia	马蓝根	Lupeol	13098	T0122	Estrogen receptor
I. indigotica	板蓝根	Salicylic acid	19187	T0061	Fatty acid synthase
I. indigotica	板蓝根	Salicylic acid	19187	T0821	Ferritin, mitochondrial
I. indigotica	大青叶	Sucrose	20446	T0094	Fos-related antigen 2
B. cusia	马蓝根	Lupeol	13098	T0247	G2/mitotic-specific cyclin-B1
I. indigotica	大青叶	Sucrose	20446	T0675	Glucose-6-phosphatase
I. indigotica	大青叶	Sucrose	20446	T0485	Glutamine synthetase
I. indigotica	板蓝根	Salicylic acid	19187	T0321	Glutathione S-transferase P
B. cusia	马蓝根	Indirubin	11024	T0177	Glycogen synthase kinase-3 beta
I. indigotica	板蓝根	Indirubin	11024	T0177	Glycogen synthase kinase-3 beta
I. indigotica	大青叶	Indirubin	11024	T0177	Glycogen synthase kinase-3 beta
S. formosanus	台湾马	Indirubin	11024	T0177	Glycogen synthase kinase-3 beta

	蓝				
I. indigotica	板蓝根	Salicylic acid	19187	T1126	Golgi-associated plant pathogenesis-related protein 1
I. indigotica	板蓝根	Salicylic acid	19187	T1122	Hairy/enhancer-of-split related with YRPW motif protein 1
B. cusia	马蓝根	Tryptanthrine	22059	T0224	Hepatocyte growth factor
I. indigotica	板蓝根	Tryptanthrine	22059	T0224	Hepatocyte growth factor
I. indigotica	大青叶	Tryptanthrine	22059	T0224	Hepatocyte growth factor
I. tinctoria	欧州菘蓝	Tryptanthrine	22059	T0224	Hepatocyte growth factor
I. indigotica	大青叶	Sucrose	20446	T1164	Hexokinase-1
B. cusia	马蓝根	Acteroside	580	T0152	Intercellular adhesion molecule 1
I. indigotica	板蓝根	Salicylic acid	19187	T0665	Interferon beta
B. cusia	马蓝根	Indirubin	11024	T0275	Interferon gamma
I. indigotica	板蓝根	Indirubin	11024	T0275	Interferon gamma
I. indigotica	大青叶	Indirubin	11024	T0275	Interferon gamma
S. formosanus	台湾马蓝	Indirubin	11024	T0275	Interferon gamma
I. indigotica	大青叶	Hexadecanoic acid	9486	T0030	Interleukin-10
I. indigotica	板蓝根	Salicylic acid	19187	T0276	Interleukin-4
I. indigotica	板蓝根	Kinetin	12227	T0051	Involucrin
I. indigotica	板蓝根	Kinetin	12227	T0590	Keratin, type I cytoskeletal 10
I. indigotica	大青叶	Sucrose	20446	T0594	Lactase-phlorizin hydrolase
I. indigotica	大青叶	Sucrose	20446	T1165	Long-chain-fatty-acid--CoA ligase 1
I. indigotica	大青叶	Sucrose	20446	T1166	Long-chain-fatty-acid--CoA ligase 4
I. indigotica	板蓝根	Salicylic acid	19187	T1127	Membrane primary amine oxidase
I. indigotica	板蓝根	β-Sitosterol	19983	T0826	Microtubule-associated protein 2

I. indigotica	大青叶	β-Sitosterol	19983	T0826	Microtubule-associated protein 2
B. cusia	马蓝根	Lupeol	13098	T0251	M-phase inducer phosphatase 3
B. cusia	马蓝根	Tryptanthrine	22059	T0223	Multidrug resistance protein 1
I. indigotica	板蓝根	Tryptanthrine	22059	T0223	Multidrug resistance protein 1
I. indigotica	大青叶	Tryptanthrine	22059	T0223	Multidrug resistance protein 1
I. tinctoria	欧州菘蓝	Tryptanthrine	22059	T0223	Multidrug resistance protein 1
I. indigotica	板蓝根	Salicylic acid	19187	T0309	Neutrophil cytosol factor 1
I. indigotica	板蓝根	Salicylic acid	19187	T0614	Nuclear factor NF-kappa-B p105 subunit
I. indigotica	大青叶	Sucrose	20446	T0356	Nuclear receptor subfamily 1 group I member 3
I. indigotica	大青叶	Sucrose	20446	T1106	Pancreatic alpha-amylase
I. indigotica	大青叶	Sucrose	20446	T0125	Peroxisome proliferator-activated receptor gamma
I. indigotica	大青叶	Hexadecanoic acid	9486	T0286	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN
I. indigotica	板蓝根	Salicylic acid	19187	T0555	Plasminogen
I. indigotica	板蓝根	Salicylic acid	19187	T1123	Prolow-density lipoprotein receptor-related protein 1
I. indigotica	板蓝根	Salicylic acid	19187	T1124	Prostacyclin synthase
I. indigotica	板蓝根	β-Sitosterol	19983	T0077	Protein kinase C alpha type
I. indigotica	大青叶	β-Sitosterol	19983	T0077	Protein kinase C alpha type
I. indigotica	大青叶	Sucrose	20446	T0015	Proto-oncogene c-Fos
I. indigotica	大青叶	Hexadecanoic acid	9486	T0814	Putative beta-glucuronidase-like protein SMA3
I. indigotica	板蓝根	Salicylic acid	19187	T0408	Pyruvate kinase isozymes R/L
B. cusia	马蓝根	Indirubin	11024	T0582	Ribosyldihydronicotinamide dehydrogenase [quinone]
I. indigotica	板蓝根	Indirubin	11024	T0582	Ribosyldihydronicotinamide

					dehydrogenase [quinone]
I. indigotica	大青叶	Indirubin	11024	T0582	Ribosyldihydronicotinamide dehydrogenase [quinone]
S. formosanus	台湾马蓝	Indirubin	11024	T0582	Ribosyldihydronicotinamide dehydrogenase [quinone]
B. cusia	马蓝根	Lupeol	13098	T0518	Serine/threonine-protein kinase PLK1
I. indigotica	板蓝根	Salicylic acid	19187	T0379	Serum paraoxonase/arylesterase 1
I. indigotica	板蓝根	β-Sitosterol	19983	T0379	Serum paraoxonase/arylesterase 1
I. indigotica	大青叶	β-Sitosterol	19983	T0379	Serum paraoxonase/arylesterase 1
I. indigotica	大青叶	Hexadecanoic acid	9486	T1101	Solute carrier family 22 member 5
I. indigotica	大青叶	Sucrose	20446	T0465	Sterol regulatory element-binding protein 1
I. indigotica	大青叶	Sucrose	20446	T0132	Sterol regulatory element-binding protein 2
I. indigotica	大青叶	Sucrose	20446	T0593	Sucrase-isomaltase, intestinal
B. cusia	马蓝根	Lupeol	13098	T0074	Superoxide dismutase [Cu-Zn]
I. indigotica	板蓝根	Salicylic acid	19187	T0074	Superoxide dismutase [Cu-Zn]
I. indigotica	板蓝根	Salicylic acid	19187	T1128	Telomeric repeat-binding factor 1
I. indigotica	板蓝根	Salicylic acid	19187	T1008	Thyroid peroxidase
I. indigotica	板蓝根	β-Sitosterol	19983	T0038	Transcription factor AP-1
I. indigotica	大青叶	β-Sitosterol	19983	T0038	Transcription factor AP-1
I. indigotica	板蓝根	Salicylic acid	19187	T0002	Transcription factor p65
I. indigotica	板蓝根	β-Sitosterol	19983	T0226	Transforming growth factor beta-1
I. indigotica	大青叶	β-Sitosterol	19983	T0226	Transforming growth factor beta-1
I. indigotica	大青叶	Hexadecanoic acid	9486	T0037	Tumor necrosis factor
I. indigotica	板蓝根	Salicylic acid	19187	T1125	Tyrosine aminotransferase
B. cusia cusia]	马蓝根	(+)-5,5'-Dimethoxy-9-O-β-D-glucopyranosyl lariciresinol	6230	NA	
B. cusia cusia]	马蓝根	(+)-5,5'-Dimethoxy-9-O-β-D-glucopyranosyl secoisolariciresinol	6231	NA	

B. cusia cusia]	马蓝根	(+)-Lyoniresinol-2α-O-β-D-glucopyranoside (D4)	13250	NA	
B. cusia cusia]	马蓝根	(+)-Lyoniresinol-3α-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranoside	13251	NA	
I. indigotica	板蓝根	(E)-2-[(3'-Indole)cyanomethylene]-3-indolinone	11030	NA	
I. indigotica	板蓝根	(E)-3-(3',5'-Dimethoxy-4'-hydroxybenzylidene)-2-indolinone	6235	NA	
I. indigotica	大青叶	1-Thiocyanato-2-hydroxy-3-butene	21334	NA	
I. indigotica	板蓝根	2,3-Dihydro-4-hydroxy-2-indole-3-acetonitrile	5637	NA	
I. indigotica	板蓝根	3-(2'-Hydroxyphenyl)-4-(3H)-quinazolinone	10643	NA	
I. indigotica	板蓝根	4-(1,2,3-Trihydroxypropyl)-2,6-dimethoxyphenyl-1-O-β-D-glucopyranoside	21840	NA	
I. indigotica	板蓝根	Adenine nucleoside	618	NA	
I. indigotica	大青叶	Adenine nucleoside	618	NA	
I. indigotica	板蓝根	Benzoic acid	2224	NA	
B. cusia	马蓝根	Cusianoside A	4419	NA	
B. cusia	马蓝根	Cusianoside B	4420	NA	
I. indigotica	大青叶	Glucobrassicin	8589	NA	
I. indigotica	大青叶	Glucobrassicin-1-Sulfonate	8590	NA	
I. indigotica	板蓝根	Indican glucoside	11014	NA	
I. indigotica	大青叶	Indican glucoside	11014	NA	
I. indigotica	板蓝根	Indigotiisocoumarin A	11022	NA	
I. indigotica	板蓝根	Indigotin	11023	NA	
I. indigotica	大青叶	Indigotin	11023	NA	
S. formosanus	台湾马蓝	Indigotin	11023	NA	
I. indigotica	板蓝根	Indole-3-acetonitrile-6-O-β-D-glucopyranoside	11028	NA	
I. indigotica	板蓝根	Isaindigodione	11186	NA	
I. indigotica	板蓝根	Isaindigotidione	11187	NA	

I. indigotica	大青叶	Isatan B	11188	NA	
I. indigotica	板蓝根	Isatin	11190	NA	
B. cusia	马蓝根	Isoindigo	11463	NA	
I. indigotica	大青叶	Neoglucobrassicin	15400	NA	
B. cusia	马蓝叶	Qingdainone	18287	NA	
I. indigotica	大青叶	Qingdainone	18287	NA	
I. tinctoria	欧州菘蓝	Qingdainone	18287	NA	
I. indigotica	板蓝根	Sinalbine	19909	NA	
I. indigotica	板蓝根	Sinigrin	19935	NA	
I. indigotica	板蓝根	Syringic acid	20566	NA	
I. indigotica	大青叶	Tryptophan	22060	NA	
I. indigotica	板蓝根	β-n-Butyl-D-tagatopyranoside	2806	NA	
I. indigotica	板蓝根	γ-Aminobutyric acid	1048	NA	
I. indigotica	板蓝根	γ-Sitosterol	19984	NA	
I. indigotica	大青叶	γ-Sitosterol	19984	NA	

Appendix 6 Biological target list for Xi shu (*Camptotheca acuminata*)

Species	Chinese	Compounds	Compound ID	Target ID	Target name
C. acuminata	喜树	Quercetin	18317	T0333	26S proteasome non-ATPase regulatory subunit 3
C. acuminata	喜树	Quercetin	18317	T0026	72 kDa type IV collagenase
C. acuminata	喜树	Quercetin	18317	T0108	78 kDa glucose-regulated protein
C. acuminata	喜树	Quercetin	18317	T0128	Acetyl-CoA carboxylase 1
C. acuminata	喜树	Quercetin	18317	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
C. acuminata	喜树	Quercetin	18317	T0114	Androgen receptor
C. acuminata	喜树	Hyperin	10887	T0018	Apoptosis regulator BAX
C. acuminata	喜树	Quercetin	18317	T0018	Apoptosis regulator BAX
C. acuminata	喜树	Quercetin	18317	T0013	Apoptosis regulator Bcl-2
C. acuminata	喜树	Quercetin	18317	T0279	Arachidonate 5-lipoxygenase
C. acuminata	喜树	Quercetin	18317	T0332	Aryl hydrocarbon receptor
C. acuminata	喜树	Quercetin	18317	T0314	ATP-binding cassette sub-family G member 2
C. acuminata	喜树	Quercetin	18317	T0202	Baculoviral IAP repeat-containing protein 5
C. acuminata	喜树	Quercetin	18317	T0014	Bcl-2-like protein 1
C. acuminata	喜树	Quercetin	18317	T0289	Bone morphogenetic protein 2
C. acuminata	喜树	Hyperin	10887	T0045	Caspase-3
C. acuminata	喜树	Quercetin	18317	T0045	Caspase-3
C. acuminata	喜树	Quercetin	18317	T0060	Caspase-8
C. acuminata	喜树	Quercetin	18317	T0019	Caspase-9
C. acuminata	喜树	Hyperin	10887	T0075	Catalase

C. acuminata	喜树	Quercetin	18317	T0075	Catalase
C. acuminata	喜树	Quercetin	18317	T0372	Cathepsin D
C. acuminata	喜树	Quercetin	18317	T0140	Caveolin-1
C. acuminata	喜树	Quercetin	18317	T0167	C-C motif chemokine 2
C. acuminata	喜树	Quercetin	18317	T0376	CD40 ligand
C. acuminata	喜树	Quercetin	18317	T0100	Cell division control protein 2 homolog
C. acuminata	喜树	Quercetin	18317	T0046	Cellular tumor antigen p53
C. acuminata	喜树	Quercetin	18317	T0359	Claudin-4
C. acuminata	喜树	Quercetin	18317	T0267	Collagen alpha-1(I) chain
C. acuminata	喜树	Quercetin	18317	T0344	Collagen alpha-1(III) chain
C. acuminata	喜树	Quercetin	18317	T0363	C-reactive protein
C. acuminata	喜树	Quercetin	18317	T0364	C-X-C motif chemokine 10
C. acuminata	喜树	Quercetin	18317	T0353	C-X-C motif chemokine 11
C. acuminata	喜树	Quercetin	18317	T0354	C-X-C motif chemokine 2
C. acuminata	喜树	Quercetin	18317	T0016	Cyclin-dependent kinase inhibitor 1
C. acuminata	喜树	Quercetin	18317	T0042	Cyclin-dependent kinase inhibitor 2A, isoforms 1/2/3
C. acuminata	喜树	Quercetin	18317	T0150	Cytochrome P450 1A1
C. acuminata	喜树	Quercetin	18317	T0138	Cytochrome P450 1A2
C. acuminata	喜树	Quercetin	18317	T0240	Cytochrome P450 1B1
C. acuminata	喜树	Quercetin	18317	T0136	Cytochrome P450 3A4
C. acuminata	喜树	Quercetin	18317	T0355	DDB1- and CUL4-associated factor 5
C. acuminata	喜树	Quercetin	18317	T0352	DNA gyrase subunit B
C. acuminata	喜树	Quercetin	18317	T0062	DNA topoisomerase 1
C. acuminata	喜树	Quercetin	18317	T0307	DNA topoisomerase 2-alpha
C. acuminata	喜树	Quercetin	18317	T0205	Dual oxidase 2

C. acuminata	喜树	Quercetin	18317	T0007	Epidermal growth factor receptor
C. acuminata	喜树	Quercetin	18317	T0174	E-selectin
C. acuminata	喜树	Quercetin	18317	T0122	Estrogen receptor
C. acuminata	喜树	Quercetin	18317	T0123	Estrogen receptor beta
C. acuminata	喜树	Quercetin	18317	T0228	Estrogen sulfotransferase
C. acuminata	喜树	Quercetin	18317	T0049	ETS domain-containing protein Elk-1
C. acuminata	喜树	Quercetin	18317	T0017	Eukaryotic translation initiation factor 6
C. acuminata	喜树	Quercetin	18317	T0375	Extracellular superoxide dismutase [Cu-Zn]
C. acuminata	喜树	Quercetin	18317	T0012	G1/S-specific cyclin-D1
C. acuminata	喜树	Quercetin	18317	T0247	G2/mitotic-specific cyclin-B1
C. acuminata	喜树	Quercetin	18317	T0145	Gap junction alpha-1 protein
C. acuminata	喜树	Quercetin	18317	T0645	Glutathione S-transferase Mu 1
C. acuminata	喜树	Quercetin	18317	T0646	Glutathione S-transferase Mu 2
C. acuminata	喜树	Quercetin	18317	T0321	Glutathione S-transferase P
C. acuminata	喜树	Quercetin	18317	T0177	Glycogen synthase kinase-3 beta
C. acuminata	喜树	Quercetin	18317	T0362	Heat shock factor protein 1
C. acuminata	喜树	Quercetin	18317	T0216	Heat shock protein beta-1
C. acuminata	喜树	Quercetin	18317	T0135	Heme oxygenase 1
C. acuminata	喜树	Quercetin	18317	T0383	Hexokinase-2
C. acuminata	喜树	Quercetin	18317	T0384	Homeobox protein Nkx-3.1
C. acuminata	喜树	Quercetin	18317	T0316	Hyaluronan synthase 2
C. acuminata	喜树	Quercetin	18317	T0090	Hypoxia-inducible factor 1-alpha
C. acuminata	喜树	Quercetin	18317	T0365	Inhibitor of nuclear factor kappa-B kinase subunit alpha
C. acuminata	喜树	Quercetin	18317	T0358	Insulin receptor
C. acuminata	喜树	Quercetin	18317	T0374	Insulin-like growth factor II

C. acuminata	喜树	Quercetin	18317	T0373	Insulin-like growth factor-binding protein 3
C. acuminata	喜树	Quercetin	18317	T0152	Intercellular adhesion molecule 1
C. acuminata	喜树	Quercetin	18317	T0275	Interferon gamma
C. acuminata	喜树	Quercetin	18317	T0377	Interferon regulatory factor 1
C. acuminata	喜树	Quercetin	18317	T0297	Interleukin-1 alpha
C. acuminata	喜树	Quercetin	18317	T0156	Interleukin-1 beta
C. acuminata	喜树	Quercetin	18317	T0030	Interleukin-10
C. acuminata	喜树	Quercetin	18317	T0231	Interleukin-2
C. acuminata	喜树	Quercetin	18317	T0039	Interleukin-6
C. acuminata	喜树	Quercetin	18317	T0181	Interleukin-8
C. acuminata	喜树	Quercetin	18317	T0086	Interstitial collagenase
C. acuminata	喜树	Quercetin	18317	T0229	Maltase-glucoamylase, intestinal
C. acuminata	喜树	Quercetin	18317	T0027	Matrix metalloproteinase-9
C. acuminata	喜树	Quercetin	18317	T0029	Mitogen-activated protein kinase 1
C. acuminata	喜树	Quercetin	18317	T0142	Myc proto-oncogene protein
C. acuminata	喜树	Quercetin	18317	T0302	Myeloperoxidase
C. acuminata	喜树	Quercetin	18317	T0323	NAD(P)H dehydrogenase [quinone] 1
C. acuminata	喜树	Hyperin	10887	T0459	NAD-dependent deacetylase sirtuin-1
C. acuminata	喜树	Quercetin	18317	T0057	NADPH--cytochrome P450 reductase
C. acuminata	喜树	Quercetin	18317	T0309	Neutrophil cytosol factor 1
C. acuminata	喜树	Quercetin	18317	T0055	NF-kappa-B inhibitor alpha
C. acuminata	喜树	Quercetin	18317	T0206	Nitric oxide synthase, endothelial
C. acuminata	喜树	Quercetin	18317	T0040	Nitric oxide synthase, inducible
C. acuminata	喜树	Quercetin	18317	T0322	Nuclear factor erythroid 2-related factor 2
C. acuminata	喜树	Quercetin	18317	T0234	Nuclear receptor subfamily 1 group I member 2

C. acuminata	喜树	Quercetin	18317	T0356	Nuclear receptor subfamily 1 group I member 3
C. acuminata	喜树	Quercetin	18317	T0058	Ornithine decarboxylase
C. acuminata	喜树	Quercetin	18317	T0366	Osteopontin
C. acuminata	喜树	Quercetin	18317	T0598	Peroxidase C1A
C. acuminata	喜树	Quercetin	18317	T0360	Peroxisome proliferator-activated receptor alpha
C. acuminata	喜树	Quercetin	18317	T0361	Peroxisome proliferator-activated receptor delta
C. acuminata	喜树	Quercetin	18317	T0125	Peroxisome proliferator-activated receptor gamma
C. acuminata	喜树	Quercetin	18317	T0286	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN
C. acuminata	喜树	Quercetin	18317	T0265	Plasminogen activator inhibitor 1
C. acuminata	喜树	Quercetin	18317	T0330	Poly [ADP-ribose] polymerase 1
C. acuminata	喜树	Quercetin	18317	T0099	Probable E3 ubiquitin-protein ligase HERC5
C. acuminata	喜树	Quercetin	18317	T0381	Procollagen C-endopeptidase enhancer 1
C. acuminata	喜树	Quercetin	18317	T0031	Pro-epidermal growth factor
C. acuminata	喜树	Quercetin	18317	T0178	Prostaglandin E2 receptor EP3 subtype
C. acuminata	喜树	Quercetin	18317	T0179	Prostaglandin G/H synthase 1
C. acuminata	喜树	Quercetin	18317	T0054	Prostaglandin G/H synthase 2
C. acuminata	喜树	Quercetin	18317	T0371	Prostatic acid phosphatase
C. acuminata	喜树	Quercetin	18317	T0098	Protein CBFA2T1
C. acuminata	喜树	Quercetin	18317	T0077	Protein kinase C alpha type
C. acuminata	喜树	Quercetin	18317	T0194	Protein kinase C beta type
C. acuminata	喜树	Quercetin	18317	T0015	Proto-oncogene c-Fos
C. acuminata	喜树	Quercetin	18317	T0382	Puromycin-sensitive aminopeptidase
C. acuminata	喜树	Quercetin	18317	T0009	RAC-alpha serine/threonine-protein kinase
C. acuminata	喜树	Quercetin	18317	T0066	RAF proto-oncogene serine/threonine-protein kinase
C. acuminata	喜树	Quercetin	18317	T0368	Ras association domain-containing protein 1

C. acuminata	喜树	Quercetin	18317	T0385	Ras GTPase-activating protein 1
C. acuminata	喜树	Quercetin	18317	T0109	Receptor tyrosine-protein kinase erbB-2
C. acuminata	喜树	Quercetin	18317	T0378	Receptor tyrosine-protein kinase erbB-3
C. acuminata	喜树	Quercetin	18317	T0033	Retinoblastoma-associated protein
C. acuminata	喜树	Quercetin	18317	T0367	Runt-related transcription factor 2
C. acuminata	喜树	Quercetin	18317	T0357	Serine/threonine-protein kinase Chk2
C. acuminata	喜树	Quercetin	18317	T0379	Serum paraoxonase/arylesterase 1
C. acuminata	喜树	Quercetin	18317	T0092	Signal transducer and activator of transcription 1-alpha/beta
C. acuminata	喜树	Quercetin	18317	T0343	Solute carrier family 2, facilitated glucose transporter member 4
C. acuminata	喜树	Hyperin	10887	T0074	Superoxide dismutase [Cu-Zn]
C. acuminata	喜树	Quercetin	18317	T0074	Superoxide dismutase [Cu-Zn]
C. acuminata	喜树	Quercetin	18317	T0262	Thrombomodulin
C. acuminata	喜树	Quercetin	18317	T0144	Tissue factor
C. acuminata	喜树	Quercetin	18317	T0261	Tissue-type plasminogen activator
C. acuminata	喜树	Quercetin	18317	T0038	Transcription factor AP-1
C. acuminata	喜树	Quercetin	18317	T0369	Transcription factor E2F1
C. acuminata	喜树	Quercetin	18317	T0370	Transcription factor E2F2
C. acuminata	喜树	Quercetin	18317	T0002	Transcription factor p65
C. acuminata	喜树	Quercetin	18317	T0226	Transforming growth factor beta-1
C. acuminata	喜树	Quercetin	18317	T0037	Tumor necrosis factor
C. acuminata	喜树	Quercetin	18317	T0380	Type I iodothyronine deiodinase
C. acuminata	喜树	Quercetin	18317	T0025	Urokinase-type plasminogen activator
C. acuminata	喜树	Quercetin	18317	T0175	Vascular cell adhesion protein 1
C. acuminata	喜树	Quercetin	18317	T0010	Vascular endothelial growth factor A

C. acuminata	喜树	Quercetin	18317	T0059	Xanthine dehydrogenase/oxidase
C. acuminata	喜树	10-Hydroxycamptothecin	9882	NA	
C. acuminata	喜树	10-Methoxy-20-O-acetylcamptothecin	13831	NA	
C. acuminata	喜树	10-Methoxycamptothecin	13863	NA	
C. acuminata	喜树	18-Hydroxycamptothecin	9883	NA	
C. acuminata	喜树	19-O-Methylangustoline	14139	NA	
C. acuminata	喜树	20-Formylbenzo[6,7]indolizino[1,2-b]quinolin-11 (13H)-one	7896	NA	
C. acuminata	喜树	20-O-Acetylcamptothecin	341	NA	
C. acuminata	喜树	20-O-β-Glucopyranosyl 18-hydroxycamptothecin	8667	NA	
C. acuminata	喜树	3,3',4-O-Trimethyl-4'-O-β-D-glucopyranosylellagic acid	21961	NA	
C. acuminata	喜树	3,3',4-Tri-O-methyl ellagic acid	21955	NA	
C. acuminata	喜树	3,4-Methylenedioxy-3',4'-O-dimethyl-5,5'-dimethoxyellagic acid	14365	NA	
C. acuminata	喜树	3,4-Methylenedioxy-3',4'-O-dimethyl-5'-methoxyellagic acid	14366	NA	
C. acuminata	喜树	3,4-Methylenedioxy-3'-O-methyl-5'-hydroxyellagic acid	14377	NA	
C. acuminata	喜树	9-Methoxycamptothecin	13864	NA	
C. acuminata	喜树	Astragalin	1935	NA	
C. acuminata	喜树	Betulinic acid	2334	NA	
C. acuminata	喜树	Camptothecin	3053	T0062*	DNA topoisomerase 1
				T0223*	Multidrug resistance protein 1
				T0314*	ATP-binding cassette sub-family G member 2
C. acuminata	喜树	Deoxycamptothecin	5157	NA	
C. acuminata	喜树	Fructose	7971	NA	
C. acuminata	喜树	Gentialutine	8291	NA	
C. acuminata	喜树	Isoquercitrin	11642	NA	

C. acuminata	喜树	Nyssoside	15880	NA	
C. acuminata	喜树	Pumiloside	18199	NA	
C. acuminata	喜树	Strictosidinic acid	20391	NA	
C. acuminata	喜树	Trifolin	21634	NA	
C. acuminata	喜树	Vincosamide	22496	NA	

* DrugBank showed camptothecin affected these 3 targets.

Appendix 7 Biological target list for Gong lao mu (*Mahonia aqulifolium, M. shenii, M. veitchiorum, M. japonica, M. bealei, M. fortunei, M. eurybracteata, M. gracilipes, M. bodinieri*)

Species	Chinese	Compound	Compound ID	Target ID	Target name
M. japonica	华南功劳木	Coptisine	4032	T0287	Amine oxidase [flavin-containing] A
M. japonica	华南功劳叶	Coptisine	4032	T0287	Amine oxidase [flavin-containing] A
M. bealei	十大功劳木	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. bodinieri	小果十大功劳	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. eurybracteata	宽苞十大功劳	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. fortunei	细叶功劳木	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. gracilipes	细柄十大功劳	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. japonica	华南功劳木	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. shenii	城口十大功劳	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M. veitchiorum	川滇十大功劳	Jatrorrhizine	11851	T0287	Amine oxidase [flavin-containing] A
M.a bealei	十大功劳木	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. bodinieri	小果十大功劳	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. eurybracteata	宽苞十大功劳	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M.a fortunei	细叶功劳木	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. gracilipes	细柄十大功劳	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M.. japonica	华南功劳木	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. shenii	城口十大功劳	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. veitchiorum	川滇十大功劳	Jatrorrhizine	11851	T0288	Amine oxidase [flavin-containing] B
M. bealei	十大功劳木	Berberine	2303	T0079	Amyloid beta A4 protein
M. bodinieri	小果十大功劳	Berberine	2303	T0079	Amyloid beta A4 protein

M. eurybracteata	宽苞十大功劳	Berberine	2303	T0079	Amyloid beta A4 protein
M. fortunei	细叶功劳木	Berberine	2303	T0079	Amyloid beta A4 protein
M. gracilipes	细柄十大功劳	Berberine	2303	T0079	Amyloid beta A4 protein
M. japonica	华南功劳木	Berberine	2303	T0079	Amyloid beta A4 protein
M. shenii	城口十大功劳	Berberine	2303	T0079	Amyloid beta A4 protein
M. veitchiorum	川滇十大功劳	Berberine	2303	T0079	Amyloid beta A4 protein
M. bealei	十大功劳木	Berberine	2303	T0006	Angiotensinogen
M. bodinieri	小果十大功劳	Berberine	2303	T0006	Angiotensinogen
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0006	Angiotensinogen
M. fortunei	细叶功劳木	Berberine	2303	T0006	Angiotensinogen
M.a gracilipes	细柄十大功劳	Berberine	2303	T0006	Angiotensinogen
M. japonica	华南功劳木	Berberine	2303	T0006	Angiotensinogen
M. shenii	城口十大功劳	Berberine	2303	T0006	Angiotensinogen
M. veitchiorum	川滇十大功劳	Berberine	2303	T0006	Angiotensinogen
M. bealei	十大功劳木	Berberine	2303	T0018	Apoptosis regulator BAX
M. bodinieri	小果十大功劳	Berberine	2303	T0018	Apoptosis regulator BAX
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0018	Apoptosis regulator BAX
M. fortunei	细叶功劳木	Berberine	2303	T0018	Apoptosis regulator BAX
M. gracilipes	细柄十大功劳	Berberine	2303	T0018	Apoptosis regulator BAX
M. japonica	华南功劳木	Berberine	2303	T0018	Apoptosis regulator BAX
M. shenii	城口十大功劳	Berberine	2303	T0018	Apoptosis regulator BAX
M. veitchiorum	川滇十大功劳	Berberine	2303	T0018	Apoptosis regulator BAX
M. bealei	十大功劳木	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. bodinieri	小果十大功劳	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0013	Apoptosis regulator Bcl-2

M. fortunei	细叶功劳木	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. gracilipes	细柄十大功劳	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. japonica	华南功劳木	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. shenii	城口十大功劳	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. veitchiorum	川滇十大功劳	Berberine	2303	T0013	Apoptosis regulator Bcl-2
M. bealei	十大功劳木	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. bodinieri	小果十大功劳	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. fortunei	细叶功劳木	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. gracilipes	细柄十大功劳	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. japonica	华南功劳木	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. shenii	城口十大功劳	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. veitchiorum	川滇十大功劳	Berberine	2303	T0332	Aryl hydrocarbon receptor
M. bealei	十大功劳木	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M.bodinieri	小果十大功劳	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. fortunei	细叶功劳木	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. gracilipes	细柄十大功劳	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. japonica	华南功劳木	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. shenii	城口十大功劳	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. veitchiorum	川滇十大功劳	Berberine	2303	T0314	ATP-binding cassette sub-family G member 2
M. bealei	十大功劳木	Berberine	2303	T0014	Bcl-2-like protein 1
M. bodinieri	小果十大功劳	Berberine	2303	T0014	Bcl-2-like protein 1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0014	Bcl-2-like protein 1
M. fortunei	细叶功劳木	Berberine	2303	T0014	Bcl-2-like protein 1

M. gracilipes	细柄十大功劳	Berberine	2303	T0014	Bcl-2-like protein 1
M. japonica	华南功劳木	Berberine	2303	T0014	Bcl-2-like protein 1
M. shenii	城口十大功劳	Berberine	2303	T0014	Bcl-2-like protein 1
M. veitchiorum	川滇十大功劳	Berberine	2303	T0014	Bcl-2-like protein 1
M. bealei	十大功劳木	Berberine	2303	T0183	BH3-interacting domain death agonist
M. bodinieri	小果十大功劳	Berberine	2303	T0183	BH3-interacting domain death agonist
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0183	BH3-interacting domain death agonist
M. fortunei	细叶功劳木	Berberine	2303	T0183	BH3-interacting domain death agonist
M. gracilipes	细柄十大功劳	Berberine	2303	T0183	BH3-interacting domain death agonist
M. japonica	华南功劳木	Berberine	2303	T0183	BH3-interacting domain death agonist
M. shenii	城口十大功劳	Berberine	2303	T0183	BH3-interacting domain death agonist
M. veitchiorum	川滇十大功劳	Berberine	2303	T0183	BH3-interacting domain death agonist
M. bealei	十大功劳木	Berberine	2303	T0045	Caspase-3
M. bodinieri	小果十大功劳	Berberine	2303	T0045	Caspase-3
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0045	Caspase-3
M. fortunei	细叶功劳木	Berberine	2303	T0045	Caspase-3
M. gracilipes	细柄十大功劳	Berberine	2303	T0045	Caspase-3
M. japonica	华南功劳木	Berberine	2303	T0045	Caspase-3
M. shenii	城口十大功劳	Berberine	2303	T0045	Caspase-3
M. veitchiorum	川滇十大功劳	Berberine	2303	T0045	Caspase-3
M. bealei	十大功劳木	Berberine	2303	T0060	Caspase-8
M. bodinieri	小果十大功劳	Berberine	2303	T0060	Caspase-8
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0060	Caspase-8
M. fortunei	细叶功劳木	Berberine	2303	T0060	Caspase-8
M. gracilipes	细柄十大功劳	Berberine	2303	T0060	Caspase-8

M. japonica	华南功劳木	Berberine	2303	T0060	Caspase-8
M. shenii	城口十大功劳	Berberine	2303	T0060	Caspase-8
M. veitchiorum	川滇十大功劳	Berberine	2303	T0060	Caspase-8
M. bealei	十大功劳木	Berberine	2303	T0019	Caspase-9
M.a bodinieri	小果十大功劳	Berberine	2303	T0019	Caspase-9
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0019	Caspase-9
M. fortunei	细叶功劳木	Berberine	2303	T0019	Caspase-9
M. gracilipes	细柄十大功劳	Berberine	2303	T0019	Caspase-9
M. japonica	华南功劳木	Berberine	2303	T0019	Caspase-9
M. shenii	城口十大功劳	Berberine	2303	T0019	Caspase-9
M. veitchiorum	川滇十大功劳	Berberine	2303	T0019	Caspase-9
M. bealei	十大功劳木	Berberine	2303	T0167	C-C motif chemokine 2
M. bodinieri	小果十大功劳	Berberine	2303	T0167	C-C motif chemokine 2
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0167	C-C motif chemokine 2
M. fortunei	细叶功劳木	Berberine	2303	T0167	C-C motif chemokine 2
M. gracilipes	细柄十大功劳	Berberine	2303	T0167	C-C motif chemokine 2
M. japonica	华南功劳木	Berberine	2303	T0167	C-C motif chemokine 2
M. shenii	城口十大功劳	Berberine	2303	T0167	C-C motif chemokine 2
M. veitchiorum	川滇十大功劳	Berberine	2303	T0167	C-C motif chemokine 2
M. bealei	十大功劳木	Berberine	2303	T0100	Cell division control protein 2 homolog
M. bodinieri	小果十大功劳	Berberine	2303	T0100	Cell division control protein 2 homolog
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0100	Cell division control protein 2 homolog
M. fortunei	细叶功劳木	Berberine	2303	T0100	Cell division control protein 2 homolog
M. gracilipes	细柄十大功劳	Berberine	2303	T0100	Cell division control protein 2 homolog
M. japonica	华南功劳木	Berberine	2303	T0100	Cell division control protein 2 homolog

M. shenii	城口十大功劳	Berberine	2303	T0100	Cell division control protein 2 homolog
M. veitchiorum	川滇十大功劳	Berberine	2303	T0100	Cell division control protein 2 homolog
M. bealei	十大功劳木	Berberine	2303	T0490	Cell division control protein 42 homolog
M. bodinieri	小果十大功劳	Berberine	2303	T0490	Cell division control protein 42 homolog
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0490	Cell division control protein 42 homolog
M. fortunei	细叶功劳木	Berberine	2303	T0490	Cell division control protein 42 homolog
M. gracilipes	细柄十大功劳	Berberine	2303	T0490	Cell division control protein 42 homolog
M. japonica	华南功劳木	Berberine	2303	T0490	Cell division control protein 42 homolog
M. shenii	城口十大功劳	Berberine	2303	T0490	Cell division control protein 42 homolog
M. veitchiorum	川滇十大功劳	Berberine	2303	T0490	Cell division control protein 42 homolog
M. bealei	十大功劳木	Berberine	2303	T0034	Cell division protein kinase 2
M. bodinieri	小果十大功劳	Berberine	2303	T0034	Cell division protein kinase 2
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0034	Cell division protein kinase 2
M. fortunei	细叶功劳木	Berberine	2303	T0034	Cell division protein kinase 2
M.gracilipes	细柄十大功劳	Berberine	2303	T0034	Cell division protein kinase 2
M. japonica	华南功劳木	Berberine	2303	T0034	Cell division protein kinase 2
M. shenii	城口十大功劳	Berberine	2303	T0034	Cell division protein kinase 2
M. veitchiorum	川滇十大功劳	Berberine	2303	T0034	Cell division protein kinase 2
M. bealei	十大功劳木	Berberine	2303	T0035	Cell division protein kinase 4
M. bodinieri	小果十大功劳	Berberine	2303	T0035	Cell division protein kinase 4
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0035	Cell division protein kinase 4
M. fortunei	细叶功劳木	Berberine	2303	T0035	Cell division protein kinase 4
M. gracilipes	细柄十大功劳	Berberine	2303	T0035	Cell division protein kinase 4
M. japonica	华南功劳木	Berberine	2303	T0035	Cell division protein kinase 4
M. shenii	城口十大功劳	Berberine	2303	T0035	Cell division protein kinase 4

M.veitchiorum	川滇十大功劳	Berberine	2303	T0035	Cell division protein kinase 4
M. bealei	十大功劳木	Berberine	2303	T0046	Cellular tumor antigen p53
M. bodinieri	小果十大功劳	Berberine	2303	T0046	Cellular tumor antigen p53
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0046	Cellular tumor antigen p53
M. fortunei	细叶功劳木	Berberine	2303	T0046	Cellular tumor antigen p53
M. gracilipes	细柄十大功劳	Berberine	2303	T0046	Cellular tumor antigen p53
M. japonica	华南功劳木	Berberine	2303	T0046	Cellular tumor antigen p53
M. shenii	城口十大功劳	Berberine	2303	T0046	Cellular tumor antigen p53
M. veitchiorum	川滇十大功劳	Berberine	2303	T0046	Cellular tumor antigen p53
M. bealei	十大功劳木	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. bodinieri	小果十大功劳	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. fortunei	细叶功劳木	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. gracilipes	细柄十大功劳	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. japonica	华南功劳木	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. shenii	城口十大功劳	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. veitchiorum	川滇十大功劳	Berberine	2303	T0016	Cyclin-dependent kinase inhibitor 1
M. bealei	十大功劳木	Berberine	2303	T0455	Cytochrome c
M. bodinieri	小果十大功劳	Berberine	2303	T0455	Cytochrome c
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0455	Cytochrome c
M. fortunei	细叶功劳木	Berberine	2303	T0455	Cytochrome c
M. gracilipes	细柄十大功劳	Berberine	2303	T0455	Cytochrome c
M. japonica	华南功劳木	Berberine	2303	T0455	Cytochrome c
M. shenii	城口十大功劳	Berberine	2303	T0455	Cytochrome c
M. veitchiorum	川滇十大功劳	Berberine	2303	T0455	Cytochrome c

M. bealei	十大功劳木	Berberine	2303	T0150	Cytochrome P450 1A1
M. bodinieri	小果十大功劳	Berberine	2303	T0150	Cytochrome P450 1A1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0150	Cytochrome P450 1A1
M. fortunei	细叶功劳木	Berberine	2303	T0150	Cytochrome P450 1A1
M. gracilipes	细柄十大功劳	Berberine	2303	T0150	Cytochrome P450 1A1
M. japonica	华南功劳木	Berberine	2303	T0150	Cytochrome P450 1A1
M. shenii	城口十大功劳	Berberine	2303	T0150	Cytochrome P450 1A1
M. veitchiorum	川滇十大功劳	Berberine	2303	T0150	Cytochrome P450 1A1
M. bealei	十大功劳木	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. bodinieri	小果十大功劳	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. fortunei	细叶功劳木	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. gracilipes	细柄十大功劳	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. japonica	华南功劳木	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. shenii	城口十大功劳	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. veitchiorum	川滇十大功劳	Berberine	2303	T0777	Delta-1-pyrroline-5-carboxylate synthase
M. bealei	十大功劳木	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. bodinieri	小果十大功劳	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. fortunei	细叶功劳木	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. gracilipes	细柄十大功劳	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. japonica	华南功劳木	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. shenii	城口十大功劳	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. veitchiorum	川滇十大功劳	Berberine	2303	T0253	DNA damage-inducible transcript 3 protein
M. bealei	十大功劳木	Berberine	2303	T0780	Early activation antigen CD69

M. bodinieri	小果十大功劳	Berberine	2303	T0780	Early activation antigen CD69
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0780	Early activation antigen CD69
M. fortunei	细叶功劳木	Berberine	2303	T0780	Early activation antigen CD69
M. gracilipes	细柄十大功劳	Berberine	2303	T0780	Early activation antigen CD69
M. japonica	华南功劳木	Berberine	2303	T0780	Early activation antigen CD69
M. shenii	城口十大功劳	Berberine	2303	T0780	Early activation antigen CD69
M. veitchiorum	川滇十大功劳	Berberine	2303	T0780	Early activation antigen CD69
M..bealei	十大功劳木	Berberine	2303	T0022	Early growth response protein 1
M. bodinieri	小果十大功劳	Berberine	2303	T0022	Early growth response protein 1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0022	Early growth response protein 1
M. fortunei	细叶功劳木	Berberine	2303	T0022	Early growth response protein 1
M. gracilipes	细柄十大功劳	Berberine	2303	T0022	Early growth response protein 1
M. japonica	华南功劳木	Berberine	2303	T0022	Early growth response protein 1
M. shenii	城口十大功劳	Berberine	2303	T0022	Early growth response protein 1
M. veitchiorum	川滇十大功劳	Berberine	2303	T0022	Early growth response protein 1
M. bealei	十大功劳木	Berberine	2303	T0007	Epidermal growth factor receptor
M. bodinieri	小果十大功劳	Berberine	2303	T0007	Epidermal growth factor receptor
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0007	Epidermal growth factor receptor
M. fortunei	细叶功劳木	Berberine	2303	T0007	Epidermal growth factor receptor
M. gracilipes	细柄十大功劳	Berberine	2303	T0007	Epidermal growth factor receptor
M. japonica	华南功劳木	Berberine	2303	T0007	Epidermal growth factor receptor
M. shenii	城口十大功劳	Berberine	2303	T0007	Epidermal growth factor receptor
M. veitchiorum	川滇十大功劳	Berberine	2303	T0007	Epidermal growth factor receptor
M. bealei	十大功劳木	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. bodinieri	小果十大功劳	Berberine	2303	T0017	Eukaryotic translation initiation factor 6

M. eurybracteata	宽苞十大功劳	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M.fortunei	细叶功劳木	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. gracilipes	细柄十大功劳	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. japonica	华南功劳木	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. shenii	城口十大功劳	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. veitchiorum	川滇十大功劳	Berberine	2303	T0017	Eukaryotic translation initiation factor 6
M. bealei	十大功劳木	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. bodinieri	小果十大功劳	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. fortunei	细叶功劳木	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. gracilipes	细柄十大功劳	Berberine	2303	T0012	G1/S-specific cyclin-D1
M.japonica	华南功劳木	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. shenii	城口十大功劳	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. veitchiorum	川滇十大功劳	Berberine	2303	T0012	G1/S-specific cyclin-D1
M. japonica	华南功劳木	Coptisine	4032	T0012	G1/S-specific cyclin-D1
M. japonica	华南功劳叶	Coptisine	4032	T0012	G1/S-specific cyclin-D1
M. bealei	十大功劳木	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M. bodinieri	小果十大功劳	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M. eurybracteata	宽苞十大功劳	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M. fortunei	细叶功劳木	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M.gracilipes	细柄十大功劳	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M.japonica	华南功劳木	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M.shenii	城口十大功劳	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0247	G2/mitotic-specific cyclin-B1
M.bealei	十大功劳木	Berberine	2303	T0774	Galanin

M.bodinieri	小果十大功劳	Berberine	2303	T0774	Galanin
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0774	Galanin
M.fortunei	细叶功劳木	Berberine	2303	T0774	Galanin
M.gracilipes	细柄十大功劳	Berberine	2303	T0774	Galanin
M.japonica	华南功劳木	Berberine	2303	T0774	Galanin
M.shenii	城口十大功劳	Berberine	2303	T0774	Galanin
M.veitchiorum	川滇十大功劳	Berberine	2303	T0774	Galanin
M.bealei	十大功劳木	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.bodinieri	小果十大功劳	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.fortunei	细叶功劳木	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.gracilipes	细柄十大功劳	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.japonica	华南功劳木	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.shenii	城口十大功劳	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.veitchiorum	川滇十大功劳	Berberine	2303	T0775	Hepatocyte nuclear factor 4-alpha
M.bealei	十大功劳木	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.bodinieri	小果十大功劳	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.fortunei	细叶功劳木	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.gracilipes	细柄十大功劳	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.japonica	华南功劳木	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.shenii	城口十大功劳	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.veitchiorum	川滇十大功劳	Berberine	2303	T0090	Hypoxia-inducible factor 1-alpha
M.bealei	十大功劳木	Berberine	2303	T0506	Insulin
M.bodinieri	小果十大功劳	Berberine	2303	T0506	Insulin

M.eurybracteata	宽苞十大功劳	Berberine	2303	T0506	Insulin
M.fortunei	细叶功劳木	Berberine	2303	T0506	Insulin
M.gracilipes	细柄十大功劳	Berberine	2303	T0506	Insulin
M.japonica	华南功劳木	Berberine	2303	T0506	Insulin
M.shenii	城口十大功劳	Berberine	2303	T0506	Insulin
M.veitchiorum	川滇十大功劳	Berberine	2303	T0506	Insulin
M.bealei	十大功劳木	Berberine	2303	T0275	Interferon gamma
M.bodinieri	小果十大功劳	Berberine	2303	T0275	Interferon gamma
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0275	Interferon gamma
M.fortunei	细叶功劳木	Berberine	2303	T0275	Interferon gamma
M.gracilipes	细柄十大功劳	Berberine	2303	T0275	Interferon gamma
M.japonica	华南功劳木	Berberine	2303	T0275	Interferon gamma
M.shenii	城口十大功劳	Berberine	2303	T0275	Interferon gamma
M.veitchiorum	川滇十大功劳	Berberine	2303	T0275	Interferon gamma
M.bealei	十大功劳木	Berberine	2303	T0156	Interleukin-1 beta
M.bodinieri	小果十大功劳	Berberine	2303	T0156	Interleukin-1 beta
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0156	Interleukin-1 beta
M.fortunei	细叶功劳木	Berberine	2303	T0156	Interleukin-1 beta
M.gracilipes	细柄十大功劳	Berberine	2303	T0156	Interleukin-1 beta
M.japonica	华南功劳木	Berberine	2303	T0156	Interleukin-1 beta
M.shenii	城口十大功劳	Berberine	2303	T0156	Interleukin-1 beta
M.veitchiorum	川滇十大功劳	Berberine	2303	T0156	Interleukin-1 beta
M.bealei	十大功劳木	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.bodinieri	小果十大功劳	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha

M.fortunei	细叶功劳木	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.gracilipes	细柄十大功劳	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.japonica	华南功劳木	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.shenii	城口十大功劳	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.veitchiorum	川滇十大功劳	Berberine	2303	T0429	Interleukin-2 receptor subunit alpha
M.bealei	十大功劳木	Berberine	2303	T0276	Interleukin-4
M.bodinieri	小果十大功劳	Berberine	2303	T0276	Interleukin-4
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0276	Interleukin-4
M.fortunei	细叶功劳木	Berberine	2303	T0276	Interleukin-4
M.gracilipes	细柄十大功劳	Berberine	2303	T0276	Interleukin-4
M.japonica	华南功劳木	Berberine	2303	T0276	Interleukin-4
M.shenii	城口十大功劳	Berberine	2303	T0276	Interleukin-4
M.veitchiorum	川滇十大功劳	Berberine	2303	T0276	Interleukin-4
M.bealei	十大功劳木	Berberine	2303	T0039	Interleukin-6
M.bodinieri	小果十大功劳	Berberine	2303	T0039	Interleukin-6
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0039	Interleukin-6
M.fortunei	细叶功劳木	Berberine	2303	T0039	Interleukin-6
M.gracilipes	细柄十大功劳	Berberine	2303	T0039	Interleukin-6
M.japonica	华南功劳木	Berberine	2303	T0039	Interleukin-6
M.shenii	城口十大功劳	Berberine	2303	T0039	Interleukin-6
M.veitchiorum	川滇十大功劳	Berberine	2303	T0039	Interleukin-6
M.bealei	十大功劳木	Berberine	2303	T0181	Interleukin-8
M.bodinieri	小果十大功劳	Berberine	2303	T0181	Interleukin-8
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0181	Interleukin-8
M.fortunei	细叶功劳木	Berberine	2303	T0181	Interleukin-8

M.gracilipes	细柄十大功劳	Berberine	2303	T0181	Interleukin-8
M.japonica	华南功劳木	Berberine	2303	T0181	Interleukin-8
M.shenii	城口十大功劳	Berberine	2303	T0181	Interleukin-8
M.veitchiorum	川滇十大功劳	Berberine	2303	T0181	Interleukin-8
M.bealei	十大功劳木	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.bodinieri	小果十大功劳	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.fortunei	细叶功劳木	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.gracilipes	细柄十大功劳	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.japonica	华南功劳木	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.shenii	城口十大功劳	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.veitchiorum	川滇十大功劳	Berberine	2303	T0229	Maltase-glucoamylase, intestinal
M.bealei	十大功劳木	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.bodinieri	小果十大功劳	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.fortunei	细叶功劳木	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.gracilipes	细柄十大功劳	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.japonica	华南功劳木	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.shenii	城口十大功劳	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0029	Mitogen-activated protein kinase 1
M.bealei	十大功劳木	Berberine	2303	T0302	Myeloperoxidase
M.bodinieri	小果十大功劳	Berberine	2303	T0302	Myeloperoxidase
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0302	Myeloperoxidase
M.fortunei	细叶功劳木	Berberine	2303	T0302	Myeloperoxidase
M.gracilipes	细柄十大功劳	Berberine	2303	T0302	Myeloperoxidase

M.japonica	华南功劳木	Berberine	2303	T0302	Myeloperoxidase
M.shenii	城口十大功劳	Berberine	2303	T0302	Myeloperoxidase
M.veitchiorum	川滇十大功劳	Berberine	2303	T0302	Myeloperoxidase
M.bealei	十大功劳木	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.bodinieri	小果十大功劳	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.fortunei	细叶功劳木	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.gracilipes	细柄十大功劳	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.japonica	华南功劳木	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.shenii	城口十大功劳	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.veitchiorum	川滇十大功劳	Berberine	2303	T0055	NF-kappa-B inhibitor alpha
M.bealei	十大功劳木	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.bodinieri	小果十大功劳	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.fortunei	细叶功劳木	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.gracilipes	细柄十大功劳	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.japonica	华南功劳木	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.shenii	城口十大功劳	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.veitchiorum	川滇十大功劳	Berberine	2303	T0040	Nitric oxide synthase, inducible
M.bealei	十大功劳木	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.bodinieri	小果十大功劳	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.fortunei	细叶功劳木	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.gracilipes	细柄十大功劳	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.japonica	华南功劳木	Berberine	2303	T0778	Platelet-derived growth factor subunit A

M.shenii	城口十大功劳	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.veitchiorum	川滇十大功劳	Berberine	2303	T0778	Platelet-derived growth factor subunit A
M.bealei	十大功劳木	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.bodinieri	小果十大功劳	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.fortunei	细叶功劳木	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.gracilipes	细柄十大功劳	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.japonica	华南功劳木	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.shenii	城口十大功劳	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.veitchiorum	川滇十大功劳	Berberine	2303	T0099	Probable E3 ubiquitin-protein ligase HERC5
M.bealei	十大功劳木	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.bodinieri	小果十大功劳	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.fortunei	细叶功劳木	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.gracilipes	细柄十大功劳	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.japonica	华南功劳木	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.shenii	城口十大功劳	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.veitchiorum	川滇十大功劳	Berberine	2303	T0776	Proprotein convertase subtilisin/kexin type 9
M.bealei	十大功劳木	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.bodinieri	小果十大功劳	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.fortunei	细叶功劳木	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.gracilipes	细柄十大功劳	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.japonica	华南功劳木	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.shenii	城口十大功劳	Berberine	2303	T0054	Prostaglandin G/H synthase 2

M.veitchiorum	川滇十大功劳	Berberine	2303	T0054	Prostaglandin G/H synthase 2
M.bealei	十大功劳木	Berberine	2303	T0098	Protein CBFA2T1
M.bodinieri	小果十大功劳	Berberine	2303	T0098	Protein CBFA2T1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0098	Protein CBFA2T1
M.fortunei	细叶功劳木	Berberine	2303	T0098	Protein CBFA2T1
M.gracilipes	细柄十大功劳	Berberine	2303	T0098	Protein CBFA2T1
M.japonica	华南功劳木	Berberine	2303	T0098	Protein CBFA2T1
M.shenii	城口十大功劳	Berberine	2303	T0098	Protein CBFA2T1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0098	Protein CBFA2T1
M.bealei	十大功劳木	Berberine	2303	T0015	Proto-oncogene c-Fos
M.bodinieri	小果十大功劳	Berberine	2303	T0015	Proto-oncogene c-Fos
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0015	Proto-oncogene c-Fos
M.fortunei	细叶功劳木	Berberine	2303	T0015	Proto-oncogene c-Fos
M.gracilipes	细柄十大功劳	Berberine	2303	T0015	Proto-oncogene c-Fos
M.japonica	华南功劳木	Berberine	2303	T0015	Proto-oncogene c-Fos
M.shenii	城口十大功劳	Berberine	2303	T0015	Proto-oncogene c-Fos
M.veitchiorum	川滇十大功劳	Berberine	2303	T0015	Proto-oncogene c-Fos
M.bealei	十大功劳木	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.bodinieri	小果十大功劳	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.fortunei	细叶功劳木	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.gracilipes	细柄十大功劳	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.japonica	华南功劳木	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.shenii	城口十大功劳	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0752	Ras-related C3 botulinum toxin substrate 1

M.bealei	十大功劳木	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.bodinieri	小果十大功劳	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.fortunei	细叶功劳木	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.gracilipes	细柄十大功劳	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.japonica	华南功劳木	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.shenii	城口十大功劳	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.veitchiorum	川滇十大功劳	Berberine	2303	T0065	Ras-specific guanine nucleotide-releasing factor 2
M.bealei	十大功劳木	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.bodinieri	小果十大功劳	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.fortunei	细叶功劳木	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.gracilipes	细柄十大功劳	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.japonica	华南功劳木	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.shenii	城口十大功劳	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0587	Solute carrier family 2, facilitated glucose transporter member 1
M.bealei	十大功劳木	Berberine	2303	T0448	Stromal cell-derived factor 1
M.bodinieri	小果十大功劳	Berberine	2303	T0448	Stromal cell-derived factor 1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0448	Stromal cell-derived factor 1
M.fortunei	细叶功劳木	Berberine	2303	T0448	Stromal cell-derived factor 1
M.gracilipes	细柄十大功劳	Berberine	2303	T0448	Stromal cell-derived factor 1
M.japonica	华南功劳木	Berberine	2303	T0448	Stromal cell-derived factor 1
M.shenii	城口十大功劳	Berberine	2303	T0448	Stromal cell-derived factor 1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0448	Stromal cell-derived factor 1
M.bealei	十大功劳木	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial

M.bodinieri	小果十大功劳	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.eurybracteata	宽苞十大功劳	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.fortunei	细叶功劳木	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.gracilipes	细柄十大功劳	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.japonica	华南功劳木	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.shenii	城口十大功劳	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.veitchiorum	川滇十大功劳	Jatrorrhizine	11851	T0319	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
M.bealei	十大功劳木	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.bodinieri	小果十大功劳	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.fortunei	细叶功劳木	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.gracilipes	细柄十大功劳	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.japonica	华南功劳木	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.shenii	城口十大功劳	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.veitchiorum	川滇十大功劳	Berberine	2303	T0593	Sucrase-isomaltase, intestinal
M.bealei	十大功劳木	Berberine	2303	T0080	Telomerase protein component 1
M.bodinieri	小果十大功劳	Berberine	2303	T0080	Telomerase protein component 1
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0080	Telomerase protein component 1
M.fortunei	细叶功劳木	Berberine	2303	T0080	Telomerase protein component 1
M.gracilipes	细柄十大功劳	Berberine	2303	T0080	Telomerase protein component 1
M.japonica	华南功劳木	Berberine	2303	T0080	Telomerase protein component 1
M.shenii	城口十大功劳	Berberine	2303	T0080	Telomerase protein component 1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0080	Telomerase protein component 1
M.bealei	十大功劳木	Berberine	2303	T0038	Transcription factor AP-1
M.bodinieri	小果十大功劳	Berberine	2303	T0038	Transcription factor AP-1

M.eurybracteata	宽苞十大功劳	Berberine	2303	T0038	Transcription factor AP-1
M.fortunei	细叶功劳木	Berberine	2303	T0038	Transcription factor AP-1
M.gracilipes	细柄十大功劳	Berberine	2303	T0038	Transcription factor AP-1
M.japonica	华南功劳木	Berberine	2303	T0038	Transcription factor AP-1
M.shenii	城口十大功劳	Berberine	2303	T0038	Transcription factor AP-1
M.veitchiorum	川滇十大功劳	Berberine	2303	T0038	Transcription factor AP-1
M.bealei	十大功劳木	Berberine	2303	T0002	Transcription factor p65
M.bodinieri	小果十大功劳	Berberine	2303	T0002	Transcription factor p65
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0002	Transcription factor p65
M.fortunei	细叶功劳木	Berberine	2303	T0002	Transcription factor p65
M.gracilipes	细柄十大功劳	Berberine	2303	T0002	Transcription factor p65
M.japonica	华南功劳木	Berberine	2303	T0002	Transcription factor p65
M.shenii	城口十大功劳	Berberine	2303	T0002	Transcription factor p65
M.veitchiorum	川滇十大功劳	Berberine	2303	T0002	Transcription factor p65
M.bealei	十大功劳木	Berberine	2303	T0037	Tumor necrosis factor
M.bodinieri	小果十大功劳	Berberine	2303	T0037	Tumor necrosis factor
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0037	Tumor necrosis factor
M.fortunei	细叶功劳木	Berberine	2303	T0037	Tumor necrosis factor
M.gracilipes	细柄十大功劳	Berberine	2303	T0037	Tumor necrosis factor
M.japonica	华南功劳木	Berberine	2303	T0037	Tumor necrosis factor
M.shenii	城口十大功劳	Berberine	2303	T0037	Tumor necrosis factor
M.veitchiorum	川滇十大功劳	Berberine	2303	T0037	Tumor necrosis factor
M.bealei	十大功劳木	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.bodinieri	小果十大功劳	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0285	Tyrosine 3-monooxygenase

M.fortunei	细叶功劳木	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.gracilipes	细柄十大功劳	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.japonica	华南功劳木	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.shenii	城口十大功劳	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.veitchiorum	川滇十大功劳	Berberine	2303	T0285	Tyrosine 3-monooxygenase
M.bealei	十大功劳木	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.bodinieri	小果十大功劳	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.eurybracteata	宽苞十大功劳	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.fortunei	细叶功劳叶	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.fortunei	细叶功劳木	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.fortunei	细叶功劳叶	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.gracilipes	细柄十大功劳	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.japonica	华南功劳木	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.japonica	华南功劳叶	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.shenii	城口十大功劳	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.veitchiorum	川滇十大功劳	Palmatine	16555	T0285	Tyrosine 3-monooxygenase
M.bealei	十大功劳木	Berberine	2303	T0010	Vascular endothelial growth factor A
M.bodinieri	小果十大功劳	Berberine	2303	T0010	Vascular endothelial growth factor A
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0010	Vascular endothelial growth factor A
M.fortunei	细叶功劳木	Berberine	2303	T0010	Vascular endothelial growth factor A
M.gracilipes	细柄十大功劳	Berberine	2303	T0010	Vascular endothelial growth factor A
M.japonica	华南功劳木	Berberine	2303	T0010	Vascular endothelial growth factor A
M.shenii	城口十大功劳	Berberine	2303	T0010	Vascular endothelial growth factor A
M.veitchiorum	川滇十大功劳	Berberine	2303	T0010	Vascular endothelial growth factor A
M.bealei	十大功劳木	Berberine	2303	T0779	Wee1-like protein kinase

M.bodinieri	小果十大功劳	Berberine	2303	T0779	Wee1-like protein kinase
M.eurybracteata	宽苞十大功劳	Berberine	2303	T0779	Wee1-like protein kinase
M.fortunei	细叶功劳木	Berberine	2303	T0779	Wee1-like protein kinase
M.gracilipes	细柄十大功劳	Berberine	2303	T0779	Wee1-like protein kinase
M.japonica	华南功劳木	Berberine	2303	T0779	Wee1-like protein kinase
M.shenii	城口十大功劳	Berberine	2303	T0779	Wee1-like protein kinase
M.veitchiorum	川滇十大功劳	Berberine	2303	T0779	Wee1-like protein kinase
M.fortunei	细叶功劳木	Berbamine	2300	NA	
M.japonica	华南功劳木	Berbamine	2300	NA	
M.japonica	华南功劳木	Columbamine	3934	NA	
M.japonica	华南功劳叶	Columbamine	3934	NA	
M.aqulifolium	尖叶十大功劳	Isocorydine	11344	NA	
M.japonica	华南功劳木	Isotetrandrine	11736	NA	
M.japonica	华南功劳叶	Isotetrandrine	11736	NA	
M.japonica	华南功劳子	Isotetrandrine	11736	NA	
M.fortunei	细叶功劳叶	Magnoflorine	13374	NA	
M.fortunei	细叶功劳木	Magnoflorine	13374	NA	
M.fortunei	细叶功劳叶	Magnoflorine	13374	NA	
M.japonica	华南功劳木	Magnoflorine	13374	NA	
M.japonica	华南功劳叶	Magnoflorine	13374	NA	
M.bealei	十大功劳叶	NA			
M.bealei	十大功劳叶	NA			
M.bealei	十大功劳子	NA			
M.aqulifolium	尖叶十大功劳	Oxyacanthine	16439	NA	
M.fortunei	细叶功劳木	Oxyacanthine	16439	NA	

Appendix 8 Biological target list for Ku shen (*Sophora flavescens*)

Species	Chinese	Compound	Compound ID	Target ID	Target name
S. flavescens	苦参	Formononetin	7883	T0638	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 1
S. flavescens	苦参	Formononetin	7883	T0637	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2
S. flavescens	苦参	Matrine	13606	T0026	72 kDa type IV collagenase
S. flavescens	苦参	Kuraridin	12341	T0317	Acyl-CoA wax alcohol acyltransferase 1
S. flavescens	苦参	Cytisine	4594	T0647	Alpha-conotoxin BuIA
S. flavescens	苦参实	Cytisine	4594	T0647	Alpha-conotoxin BuIA
S. flavescens	苦参	Matrine	13606	T0114	Androgen receptor
S. flavescens	苦参	Formononetin	7883	T0635	ATP synthase subunit beta, mitochondrial
S. flavescens	苦参	Matrine	13606	T0045	Caspase-3
S. flavescens	苦参	Matrine	13606	T0627	CD44 antigen
S. flavescens	苦参	Formononetin	7883	T0122	Estrogen receptor
S. flavescens	苦参	Formononetin	7883	T0123	Estrogen receptor beta
S. flavescens	苦参	Matrine	13606	T0396	Heparanase
S. flavescens	苦参	Matrine	13606	T0626	Immediate early response 3-interacting protein 1
S. flavescens	苦参	Matrine	13606	T0152	Intercellular adhesion molecule 1
S. flavescens	苦参	Formononetin	7883	T0276	Interleukin-4
S. flavescens	苦参	Matrine	13606	T0039	Interleukin-6
S. flavescens	苦参	Sophocarpine	20077	T0039	Interleukin-6
S. flavescens	苦参	Sophoramine	20094	T0039	Interleukin-6
S. flavescens	苦参	Sophoridine	20100	T0039	Interleukin-6

S. flavescens	苦参	Matrine	13606	T0142	Myc proto-oncogene protein
S. flavescens	苦参	Formononetin	7883	T0459	NAD-dependent deacetylase sirtuin-1
S. flavescens	苦参	Formononetin	7883	T0636	NADH-ubiquinone oxidoreductase chain 6
S. flavescens	苦参	Cytisine	4594	T0568	Neuronal acetylcholine receptor subunit alpha-7
S. flavescens	苦参实	Cytisine	4594	T0568	Neuronal acetylcholine receptor subunit alpha-7
S. flavescens	苦参	Formononetin	7883	T0125	Peroxisome proliferator-activated receptor gamma
S. flavescens	苦参	Kuraridin	12341	T0054	Prostaglandin G/H synthase 2
S. flavescens	苦参	Cytisine	4594	T0015	Proto-oncogene c-Fos
S. flavescens	苦参实	Cytisine	4594	T0015	Proto-oncogene c-Fos
S. flavescens	苦参	Formononetin	7883	T0038	Transcription factor AP-1
S. flavescens	苦参	Matrine	13606	T0002	Transcription factor p65
S. flavescens	苦参	Matrine	13606	T0037	Tumor necrosis factor
S. flavescens	苦参	Sophocarpine	20077	T0037	Tumor necrosis factor
S. flavescens	苦参	Sophoramine	20094	T0037	Tumor necrosis factor
S. flavescens	苦参	Sophoridine	20100	T0037	Tumor necrosis factor
S. flavescens	苦参	Kuraridin	12341	T0256	Tyrosinase
S. flavescens	苦参	(+)-Allomatrine	938	NA	
S. flavescens	苦参	2'-Methoxykurarinone	13985	NA	
S. flavescens	苦参	2-n-Heneicosyl-5,7-dihydroxy-6,8-dimethyl chromone	9361	NA	
S. flavescens	苦参	2-n-Heptadecy-5,7-dihydroxy-6,8-dimethyl chromone	9391	NA	
S. flavescens	苦参	2-n-Nonadecyl-5,7-dihydroxy-6,8-dimethyl chromone	15674	NA	
S. flavescens	苦参	2-n-Pentacosyl-5,7-dihydroxy-6,8-dimethyl chromone	16826	NA	
S. flavescens	苦参	2-n-Pentadecyl-5,7-dihydroxy-6,8-dimethyl chromone	16834	NA	

S. flavescens	苦参	2-n-Tridecyl-5,7-dihydroxy-6,8-dimethyl chromone	21623	NA	
S. flavescens	苦参	5-O-Methyl kushenol C	14545	NA	
S. flavescens	苦参	7,11-Dehydromatrine	4948	NA	
S. flavescens	苦参	8-Isopentenyl-kaempferol	11588	NA	
S. flavescens	苦参	9α-Hydroxysophoramine	10714	NA	
S. flavescens	苦参	Anagyrine	1134	NA	
S. flavescens	苦参	Baptifoline	2145	NA	
S. flavescens	苦参	Isoanhydroicaritin	11222	NA	
S. flavescens	苦参	Isokuraramine	11473	NA	
S. flavescens	苦参	Isokurarinone	11474	NA	
S. flavescens	苦参	Isomatrine	11531	NA	
S. flavescens	苦参	Isoxanthohumol	11783	NA	
S. flavescens	苦参	Kosamol A	12280	NA	
S. flavescens	苦参	Kosamol Q	12281	NA	
S. flavescens	苦参	Kosamol R	12282	NA	
S. flavescens	苦参	Kosamol S	12283	NA	
S. flavescens	苦参	Kosamol T	12284	NA	
S. flavescens	苦参	Kosamol U	12285	NA	
S. flavescens	苦参	Kosamol V	12286	NA	
S. flavescens	苦参	Kosamol W	12287	NA	
S. flavescens	苦参	Kuraramine	12340	NA	
S. flavescens	苦参	Kuraridinol	12342	NA	
S. flavescens	苦参	Kurarinol	12343	NA	
S. flavescens	苦参	Kurarinone	12344	NA	
S. flavescens	苦参	Kushenin	12353	NA	

S. flavescens	苦参	Kushenol A	12354	NA	
S. flavescens	苦参	Kushenol B	12355	NA	
S. flavescens	苦参	Kushenol C	12356	NA	
S. flavescens	苦参	Kushenol D	12357	NA	
S. flavescens	苦参	Kushenol E	12358	NA	
S. flavescens	苦参	Kushenol F	12359	NA	
S. flavescens	苦参	Kushenol G	12360	NA	
S. flavescens	苦参	Kushenol H	12361	NA	
S. flavescens	苦参	Kushenol I	12362	NA	
S. flavescens	苦参	Kushenol J	12363	NA	
S. flavescens	苦参	Kushenol K	12364	NA	
S. flavescens	苦参	Kushenol L	12365	NA	
S. flavescens	苦参	Kushenol M	12366	NA	
S. flavescens	苦参	Kushenol N	12367	NA	
S. flavescens	苦参	Kushenol O	12368	NA	
S. flavescens	苦参	Kushenol P	12369	NA	
S. flavescens	苦参	Kushenol X	12370	NA	
S. flavescens	苦参	Kushenquinone A	12371	NA	
S. flavescens	苦参	Leachianone A	12595	NA	
S. flavescens	苦参	Leachianone G	12597	NA	
S. flavescens	苦参	Lehmannine	12605	NA	
S. flavescens	苦参	Lupanine	13089	NA	
S. flavescens	苦参	Maackiain	13281	NA	
S. flavescens	苦参	Mamanine	13462	NA	
S. flavescens	苦参	Neokurarinol	15425	NA	

S. flavescens	苦参	N-Methylcytisine	14279	NA	
S. flavescens	苦参	Norkurarinol	15769	NA	
S. flavescens	苦参	Norkurarinone	15770	NA	
S. flavescens	苦参	N-Oxysophocarpine	16474	NA	
S. flavescens	苦参实	N-Oxysophocarpine	16474	NA	
S. flavescens	苦参	Oxymatrine	16451	NA	
S. flavescens	苦参	Sophoflavescenol	20078	NA	
S. flavescens	苦参	Sophoraflavanone G	20086	NA	
S. flavescens	苦参	Sophoraflavoside II	20090	NA	
S. flavescens	苦参	Sophoraflavoside III	20091	NA	
S. flavescens	苦参	Sophoraflavoside IV	20092	NA	
S. flavescens	苦参	SophoraflavosideI	20089	NA	
S. flavescens	苦参	Sophoranol	20096	NA	
S. flavescens	苦参	Sophoranol N-oxide	20097	NA	
S. flavescens	苦参	Soyasaponin I	20127	NA	
S. flavescens	苦参	Trifolirhizin-6"-O-malonate	21638	NA	
S. flavescens	苦参	Xanthohumol	22761	NA	
S. flavescens	苦参	α-Maackiain-β-D-glucoside	13282	NA	

Appendix 9 Biological target list for Zi cao (*Lithospermum erythrorhizon, Arnebia guttata, A. euchroma, Onosma hookeri, O. paniculatum*)

Species	**Chinese**	**Compound**	**Compound ID**	**target ID**	**target name**
L. erythrorhizon	紫草	Caffeic acid	2887	T0185	Acetylcholinesterase
A. euchroma	新藏假紫草	Shikonin	19819	T0287	Amine oxidase [flavin-containing] A
A. guttata	假紫草	Shikonin	19819	T0287	Amine oxidase [flavin-containing] A
L. erythrorhizon	紫草	Shikonin	19819	T0287	Amine oxidase [flavin-containing] A
O. paniculatum	滇紫草	Shikonin	19819	T0287	Amine oxidase [flavin-containing] A
A. euchroma	新藏假紫草	Shikonin	19819	T0288	Amine oxidase [flavin-containing] B
A. guttata	假紫草	Shikonin	19819	T0288	Amine oxidase [flavin-containing] B
L. erythrorhizon	紫草	Shikonin	19819	T0288	Amine oxidase [flavin-containing] B
O. paniculatum	滇紫草	Shikonin	19819	T0288	Amine oxidase [flavin-containing] B
A. euchroma	新藏假紫草	Shikonin	19819	T1298	Angiopoietin-1 receptor
A. guttata	假紫草	Shikonin	19819	T1298	Angiopoietin-1 receptor
L. erythrorhizon	紫草	Shikonin	19819	T1298	Angiopoietin-1 receptor
O. paniculatum	滇紫草	Shikonin	19819	T1298	Angiopoietin-1 receptor
A. euchroma	新藏假紫草	Shikonin	19819	T0013	Apoptosis regulator Bcl-2
A. guttata	假紫草	Shikonin	19819	T0013	Apoptosis regulator Bcl-2
L. erythrorhizon	紫草	Shikonin	19819	T0013	Apoptosis regulator Bcl-2
O. paniculatum	滇紫草	Shikonin	19819	T0013	Apoptosis regulator Bcl-2
A. euchroma	新藏假紫草	Shikonin	19819	T0970	Arylamine N-acetyltransferase 1
A. guttata	假紫草	Shikonin	19819	T0970	Arylamine N-acetyltransferase 1
L. erythrorhizon	紫草	Shikonin	19819	T0970	Arylamine N-acetyltransferase 1
O.paniculatum	滇紫草	Shikonin	19819	T0970	Arylamine N-acetyltransferase 1

A. euchroma	新藏假紫草	Shikonin	19819	T0072	Bcl2 antagonist of cell death
A. guttata	假紫草	Shikonin	19819	T0072	Bcl2 antagonist of cell death
L. erythrorhizon	紫草	Shikonin	19819	T0072	Bcl2 antagonist of cell death
O. paniculatum	滇紫草	Shikonin	19819	T0072	Bcl2 antagonist of cell death
A. euchroma	新藏假紫草	Shikonin	19819	T0045	Caspase-3
A. guttata	假紫草	Shikonin	19819	T0045	Caspase-3
L. erythrorhizon	紫草	Shikonin	19819	T0045	Caspase-3
O. paniculatum	滇紫草	Shikonin	19819	T0045	Caspase-3
A. euchroma	新藏假紫草	Shikonin	19819	T0434	C-C motif chemokine 3
A. guttata	假紫草	Shikonin	19819	T0434	C-C motif chemokine 3
L. erythrorhizon	紫草	Shikonin	19819	T0434	C-C motif chemokine 3
O. paniculatum	滇紫草	Shikonin	19819	T0434	C-C motif chemokine 3
A. euchroma	新藏假紫草	Shikonin	19819	T0447	C-C motif chemokine 5
A. guttata	假紫草	Shikonin	19819	T0447	C-C motif chemokine 5
L. erythrorhizon	紫草	Shikonin	19819	T0447	C-C motif chemokine 5
O. paniculatum	滇紫草	Shikonin	19819	T0447	C-C motif chemokine 5
A. euchroma	新藏假紫草	Shikonin	19819	T0046	Cellular tumor antigen p53
A. guttata	假紫草	Shikonin	19819	T0046	Cellular tumor antigen p53
L. erythrorhizon	紫草	Shikonin	19819	T0046	Cellular tumor antigen p53
O. paniculatum	滇紫草	Shikonin	19819	T0046	Cellular tumor antigen p53
L. erythrorhizon	紫草	Caffeic acid	2887	T0150	Cytochrome P450 1A1
A. euchroma	新藏假紫草	Shikonin	19819	T1300	Ephrin type-B receptor 2
A. guttata	假紫草	Shikonin	19819	T1300	Ephrin type-B receptor 2
L. erythrorhizon	紫草	Shikonin	19819	T1300	Ephrin type-B receptor 2
O. paniculatum	滇紫草	Shikonin	19819	T1300	Ephrin type-B receptor 2

A. euchroma	新藏假紫草	Shikonin	19819	T1286	Fatty acid-binding protein, adipocyte
A. guttata	假紫草	Shikonin	19819	T1286	Fatty acid-binding protein, adipocyte
L. erythrorhizon	紫草	Shikonin	19819	T1286	Fatty acid-binding protein, adipocyte
O. paniculatum	滇紫草	Shikonin	19819	T1286	Fatty acid-binding protein, adipocyte
A. euchroma	新藏假紫草	Shikonin	19819	T0012	G1/S-specific cyclin-D1
A. guttata	假紫草	Shikonin	19819	T0012	G1/S-specific cyclin-D1
L. erythrorhizon	紫草	Shikonin	19819	T0012	G1/S-specific cyclin-D1
O. paniculatum	滇紫草	Shikonin	19819	T0012	G1/S-specific cyclin-D1
L. erythrorhizon	紫草	Caffeic acid	2887	T0346	Glial fibrillary acidic protein
L. erythrorhizon	紫草	Caffeic acid	2887	T0374	Insulin-like growth factor II
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0156	Interleukin-1 beta
A. euchroma	新藏假紫草	Shikonin	19819	T0030	Interleukin-10
A. guttata	假紫草	Shikonin	19819	T0030	Interleukin-10
L. erythrorhizon	紫草	Shikonin	19819	T0030	Interleukin-10
O. paniculatum	滇紫草	Shikonin	19819	T0030	Interleukin-10
A. euchroma	新藏假紫草	Shikonin	19819	T0276	Interleukin-4
A. guttata	假紫草	Shikonin	19819	T0276	Interleukin-4
L. erythrorhizon	紫草	Shikonin	19819	T0276	Interleukin-4
O. paniculatum	滇紫草	Shikonin	19819	T0276	Interleukin-4
A. euchroma	新藏假紫草	Shikonin	19819	T0039	Interleukin-6
A. guttata	假紫草	Shikonin	19819	T0039	Interleukin-6
L. erythrorhizon	紫草	Shikonin	19819	T0039	Interleukin-6
O. paniculatum	滇紫草	Shikonin	19819	T0039	Interleukin-6
A. euchroma	新藏假紫草	Shikonin	19819	T0181	Interleukin-8
A. guttata	假紫草	Shikonin	19819	T0181	Interleukin-8

L. erythrorhizon	紫草	Shikonin	19819	T0181	Interleukin-8
O. paniculatum	滇紫草	Shikonin	19819	T0181	Interleukin-8
A. euchroma	新藏假紫草	Shikonin	19819	T0173	Lipoprotein lipase
A. guttata	假紫草	Shikonin	19819	T0173	Lipoprotein lipase
L. erythrorhizon	紫草	Shikonin	19819	T0173	Lipoprotein lipase
O. paniculatum	滇紫草	Shikonin	19819	T0173	Lipoprotein lipase
A. euchroma	新藏假紫草	Shikonin	19819	T1299	Lysyl-tRNA synthetase
A. guttata	假紫草	Shikonin	19819	T1299	Lysyl-tRNA synthetase
L. erythrorhizon	紫草	Shikonin	19819	T1299	Lysyl-tRNA synthetase
O. paniculatum	滇紫草	Shikonin	19819	T1299	Lysyl-tRNA synthetase
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0055	NF-kappa-B inhibitor alpha
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0040	Nitric oxide synthase, inducible
A. euchroma	新藏假紫草	Shikonin	19819	T0742	Nuclear receptor subfamily 4 group A member 1
A. guttata	假紫草	Shikonin	19819	T0742	Nuclear receptor subfamily 4 group A member 1
L. erythrorhizon	紫草	Shikonin	19819	T0742	Nuclear receptor subfamily 4 group A member 1
O. paniculatum	滇紫草	Shikonin	19819	T0742	Nuclear receptor subfamily 4 group A member 1
A. euchroma	新藏假紫草	Shikonin	19819	T0125	Peroxisome proliferator-activated receptor gamma
A. guttata	假紫草	Shikonin	19819	T0125	Peroxisome proliferator-activated receptor gamma
L. erythrorhizon	紫草	Shikonin	19819	T0125	Peroxisome proliferator-activated receptor gamma
O. paniculatum	滇紫草	Shikonin	19819	T0125	Peroxisome proliferator-activated receptor gamma
A. euchroma	新藏假紫草	Shikonin	19819	T0101	Proliferating cell nuclear antigen
A. guttata	假紫草	Shikonin	19819	T0101	Proliferating cell nuclear antigen
L. erythrorhizon	紫草	Shikonin	19819	T0101	Proliferating cell nuclear antigen
O. paniculatum	滇紫草	Shikonin	19819	T0101	Proliferating cell nuclear antigen
L. erythrorhizon	紫草	Caffeic acid	2887	T0179	Prostaglandin G/H synthase 1

L. erythrorhizon	紫草	Caffeic acid	2887	T0054	Prostaglandin G/H synthase 2
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0054	Prostaglandin G/H synthase 2
A. euchroma	新藏假紫草	Shikonin	19819	T1297	Proteasome subunit beta type-4
A. guttata	假紫草	Shikonin	19819	T1297	Proteasome subunit beta type-4
L. erythrorhizon	紫草	Shikonin	19819	T1297	Proteasome subunit beta type-4
O. paniculatum	滇紫草	Shikonin	19819	T1297	Proteasome subunit beta type-4
L. erythrorhizon	紫草	Caffeic acid	2887	T0194	Protein kinase C beta type
L. erythrorhizon	紫草	Caffeic acid	2887	T0388	P-selectin
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0009	RAC-alpha serine/threonine-protein kinase
A. euchroma	新藏假紫草	Shikonin	19819	T0009	RAC-alpha serine/threonine-protein kinase
A. guttata	假紫草	Shikonin	19819	T0009	RAC-alpha serine/threonine-protein kinase
L. erythrorhizon	紫草	Shikonin	19819	T0009	RAC-alpha serine/threonine-protein kinase
O. paniculatum	滇紫草	Shikonin	19819	T0009	RAC-alpha serine/threonine-protein kinase
L. erythrorhizon	紫草	Caffeic acid	2887	T0752	Ras-related C3 botulinum toxin substrate 1
A. euchroma	新藏假紫草	Shikonin	19819	T1183	Ribonuclease P protein subunit p21
A. guttata	假紫草	Shikonin	19819	T1183	Ribonuclease P protein subunit p21
L. erythrorhizon	紫草	Shikonin	19819	T1183	Ribonuclease P protein subunit p21
O. paniculatum	滇紫草	Shikonin	19819	T1183	Ribonuclease P protein subunit p21
A. euchroma	新藏假紫草	Shikonin	19819	T1301	Serine/threonine-protein kinase PAK 2
A. guttata	假紫草	Shikonin	19819	T1301	Serine/threonine-protein kinase PAK 2
L. erythrorhizon	紫草	Shikonin	19819	T1301	Serine/threonine-protein kinase PAK 2
O. paniculatum	滇紫草	Shikonin	19819	T1301	Serine/threonine-protein kinase PAK 2
A. euchroma	新藏假紫草	Shikonin	19819	T0465	Sterol regulatory element-binding protein 1
A. guttata	假紫草	Shikonin	19819	T0465	Sterol regulatory element-binding protein 1
L. erythrorhizon	紫草	Shikonin	19819	T0465	Sterol regulatory element-binding protein 1

O. paniculatum	滇紫草	Shikonin	19819	T0465	Sterol regulatory element-binding protein 1
A. euchroma	新藏假紫草	Shikonin	19819	T0277	Trans-acting T-cell-specific transcription factor GATA-3
A. guttata	假紫草	Shikonin	19819	T0277	Trans-acting T-cell-specific transcription factor GATA-3
L. erythrorhizon	紫草	Shikonin	19819	T0277	Trans-acting T-cell-specific transcription factor GATA-3
O. paniculatum	滇紫草	Shikonin	19819	T0277	Trans-acting T-cell-specific transcription factor GATA-3
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0002	Transcription factor p65
L. erythrorhizon	紫草	Caffeic acid	2887	T0037	Tumor necrosis factor
L. erythrorhizon	紫草	Isobutyryl shikonin	11300	T0037	Tumor necrosis factor
L. erythrorhizon	紫草	Caffeic acid	2887	T0326	Tyrosine-protein kinase BTK
A. euchroma	新藏假紫草	Shikonin	19819	T0021	Vascular endothelial growth factor receptor 2
A. guttata	假紫草	Shikonin	19819	T0021	Vascular endothelial growth factor receptor 2
L. erythrorhizon	紫草	Shikonin	19819	T0021	Vascular endothelial growth factor receptor 2
O.paniculatum	滇紫草	Shikonin	19819	T0021	Vascular endothelial growth factor receptor 2
A. euchroma	新藏假紫草	(−)-Alkannin	909	NA	
A. euchroma	新藏假紫草	1-Methyl-acetylshikonin	14120	NA	
L. erythrorhizon	紫草	1-Methyl-acetylshikonin	14120	NA	
A. euchroma	新藏假紫草	2α,19α-Dihydroxyursolic acid	6178	NA	
A. euchroma	新藏假紫草	3,4-Teracrylshikonin	20968	NA	
A. guttata	假紫草	3,4-Teracrylshikonin	20968	NA	
L. erythrorhizon	紫草	3,4-Teracrylshikonin	20968	NA	
A. euchroma	新藏假紫草	Acetylalkannin	309	NA	
A. guttata	假紫草	Acetylalkannin	309	NA	
L. erythrorhizon	紫草	Acetylalkannin	309	NA	
O. paniculatum	滇紫草	Acetylalkannin	309	NA	
A. euchroma	新藏假紫草	Acetylshikonin	514	NA	
A. guttata	假紫草	Acetylshikonin	514	NA	

L. erythrorhizon	紫草	Acetylshikonin	514	NA	
O. hookeri	细花滇紫草	Acetylshikonin	514	NA	
O. paniculatum	滇紫草	Acetylshikonin	514	NA	
L. erythrorhizon	紫草	Alkannan	908	NA	
L. erythrorhizon	紫草	Alkannin angelate	910	NA	
A. euchroma	新藏假紫草	Anhydroalkannin	1259	NA	
L. erythrorhizon	紫草	Anhydroalkannin	1259	NA	
A. euchroma	新藏假紫草	Arnebifuranone	1744	NA	
L. erythrorhizon	紫草	Arnebifuranone	1744	NA	
A. euchroma	新藏假紫草	Arnebinol	1746	NA	
A. euchroma	新藏假紫草	Arnebinone	1747	NA	
A. euchroma	新藏假紫草	Deoxyshikonin	5214	NA	
A. guttata	假紫草	Deoxyshikonin	5214	NA	
A. euchroma	紫草	Deoxyshikonin	5214	NA	
A. euchroma	新藏假紫草	Des-O-methyllasiodiplodin	5258	NA	
L. erythrorhizon	紫草	Des-O-methyllasiodiplodin	5258	NA	
A. euchroma	新藏假紫草	Dipotassium rabdosiin	6495	NA	
L. erythrorhizon	紫草	Docosyl caffeate	6539	NA	
L. erythrorhizon	紫草	Eicosanol	6722	NA	
L. erythrorhizon	紫草	Eicosyl caffeate	6726	NA	
L. erythrorhizon	紫草	Hydroxymyoscorpine	10535	NA	
L. erythrorhizon	紫草	Intermedine	11107	NA	
A. euchroma	新藏假紫草	Isobutyryl shikonin	11300	NA	
L. erythrorhizon	紫草	Isovalerylshikonin	11765	NA	
L. erythrorhizon	紫草	Lithospermidin A	12927	NA	

L. erythrorhizon	紫草	Lithospermidin B	12928	NA	
L. erythrorhizon	紫草	Myoscorpine	15145	NA	
A. euchroma	新藏假紫草	NP02140176-38-K	15850	NA	
L. erythrorhizon	紫草	NP02140176-38-K	15850	NA	
A. euchroma	新藏假紫草	NP02140176-39-Na	15851	NA	
L. erythrorhizon	紫草	NP02140176-39-Na	15851	NA	
A. euchroma	新藏假紫草	NP02140176-40	15852	NA	
L. erythrorhizon	紫草	NP02140176-40	15852	NA	
A. euchroma	新藏假紫草	NP02140176-41-KNa	15853	NA	
L. erythrorhizon	紫草	NP02140176-41-KNa	15853	NA	
A. euchroma	新藏假紫草	NP02140176-42-K	15854	NA	
L. erythrorhizon	紫草	NP02140176-42-K	15854	NA	
A. euchroma	新藏假紫草	O7-Angeloylretronecine	1233	NA	
L. erythrorhizon	紫草	O7-Angeloylretronecine	1233	NA	
A. euchroma	新藏假紫草	O9-Angeloylretronecine	1234	NA	
L. erythrorhizon	紫草	O9-Angeloylretronecine	1234	NA	
L. erythrorhizon	紫草	Octadecanyl caffeate	15953	NA	
A. euchroma	新藏假紫草	Potassium rosmarinate	17747	NA	
L. erythrorhizon	紫草	Propionylshikonin	17933	NA	
L. erythrorhizon	紫草	Rhizonone	18780	NA	
L. erythrorhizon	紫草	Shikonine	19820	NA	
L. erythrorhizon	紫草	Shikonofuran A	19821	NA	
A. euchroma	新藏假紫草	Shikonofuran B	19822	NA	
L. erythrorhizon	紫草	Shikonofuran B	19822	NA	
A. euchroma	新藏假紫草	Shikonofuran C	19823	NA	

L. erythrorhizon	紫草	Shikonofuran C	19823	NA	
L. erythrorhizon	紫草	Shikonofuran D	19824	NA	
L. erythrorhizon	紫草	Shikonofuran E	19825	NA	
A. euchroma	新藏假紫草	Sodium ferulate	20032	NA	
A. euchroma	新藏假紫草	Sodium rosmarinate	20036	NA	
L. erythrorhizon	紫草	Tetracosyl caffeate	21039	NA	
A. euchroma	新藏假紫草	α-Acetoxyisovalerylalkannin	244	NA	
L. erythrorhizon	紫草	α-Acetoxyisovalerylalkannin	244	NA	
L. erythrorhizon	紫草	α-Methyl-n-butyrylshikonin	14202	NA	
A. euchroma	新藏假紫草	β,β-Dimethylacrylalkannin	6302	NA	
L. erythrorhizon	紫草	β,β-Dimethylacrylalkannin	6302	NA	
O. paniculatum	滇紫草	β,β-Dimethylacrylalkannin	6302	NA	
A. euchroma	新藏假紫草	β,β-Dimethylacrylshikonin	6303	NA	
A. guttata	假紫草	β,β-Dimethylacrylshikonin	6303	NA	
L. erythrorhizon	紫草	β,β-Dimethylacrylshikonin	6303	NA	
O. paniculatum	滇紫草	β,β-Dimethylacrylshikonin	6303	NA	
A. euchroma	新藏假紫草	β-Hydroxyisovalerylshikonin	10266	NA	
A. guttata	假紫草	β-Hydroxyisovalerylshikonin	10266	NA	
L. erythrorhizon	紫草	β-Hydroxyisovalerylshikonin	10266	NA	
O. paniculatum	滇紫草	β-Hydroxyisovalerylshikonin	10266	NA	

Appendix 10 Biological target list for She chuang zi (*Cnidium monnieri*)

Species	Chinese	Compound	Compound ID	target ID	target name
C. monnieri	蛇床子	Osthole	16261	T0291	3-hydroxy-3-methylglutaryl-coenzyme A reductase
C. monnieri	蛇床子	Osthole	16261	T0044	Activator of 90 kDa heat shock protein ATPase homolog 1
C. monnieri	蛇床子	Osthole	16261	T0289	Bone morphogenetic protein 2
C. monnieri	蛇床子	Osthole	16261	T0293	Carnitine O-palmitoyltransferase 1, liver isoform
C. monnieri	蛇床子	Isopimpinellin	11601	T0150	Cytochrome P450 1A1
C. monnieri	蛇床子	Isopimpinellin	11601	T0320	Cytochrome P450 2B10
C. monnieri	蛇床子	Bergapten	2309	T0136	Cytochrome P450 3A4
C. monnieri	蛇床子	Isopimpinellin	11601	T0136	Cytochrome P450 3A4
C. monnieri	蛇床子	Isopimpinellin	11601	T0321	Glutathione S-transferase P
C. monnieri	蛇床子	Osthole	16261	T0292	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial
C. monnieri	蛇床子	Osthole	16261	T0290	Mothers against decapentaplegic homolog 1
C. monnieri	蛇床子	Osthole	16261	T0040	Nitric oxide synthase, inducible
C. monnieri	蛇床子	Isopimpinellin	11601	T0234	Nuclear receptor subfamily 1 group I member 2
C. monnieri	蛇床子	1(7),8(10)-p-Menthadien-9-ol	13725	NA	
C. monnieri	蛇床子	2'-Acetylangelicin	316	NA	
C. monnieri	蛇床子	3'-Isobutyryloxy-O-acetyl-2',3'-dihydro-oroselol	11297	NA	
C. monnieri	蛇床子	Alloimperatorin	933	NA	
C. monnieri	蛇床子	Archangelicin	1619	NA	
C. monnieri	蛇床子	Cnidiadin	3854	NA	
C. monnieri	蛇床子	Cnidioside A	3857	NA	
C. monnieri	蛇床子	Columbianadin	3935	NA	
C. monnieri	蛇床子	Columbianetin	3936	NA	

C. monnieri	蛇床子	Columbianetin acetate	3937	NA	
C. monnieri	蛇床子	D-Quinovitol	18443	NA	
C. monnieri	蛇床子	Edultin	6709	NA	
C. monnieri	蛇床子	Imperatorin	11001	NA	
C. monnieri	蛇床子	Isovaleroxy-hydroxy dihydrovaltrate	11755	NA	
C. monnieri	蛇床子	O-Isovalerylcolum bianetin	11761	NA	
C. monnieri	蛇床子	Umtatin	22203	NA	
C. monnieri	蛇床子	Xanthotoxin	22774	NA	
C. monnieri	蛇床子	Xanthotoxol	22775	NA	

Appendix 11 Biological target list for Bai xian pi (*Dictamnus dasycarpus*)

Species	Chinese	Compound	Compound ID	target ID	target name
D. dasycarpus	白鲜皮	Obaculactone	15882	T0136	Cytochrome P450 3A4
D. dasycarpus	白鲜皮	Campesterol	3040	NA	
D. dasycarpus	白鲜皮	Dasycarpamine	4663	NA	
D. dasycarpus	白鲜皮	Dictamnine	5445	NA	
D. dasycarpus	白鲜皮	Dictamnoside A	5446	NA	
D. dasycarpus	白鲜皮	Dictamnoside B	5447	NA	
D. dasycarpus	白鲜皮	Dictamnoside G	5448	NA	
D. dasycarpus	白鲜皮	Dictamnoside H	5449	NA	
D. dasycarpus	白鲜皮	Dictamnoside I	5450	NA	
D. dasycarpus	白鲜皮	Dictamnoside J	5451	NA	
D. dasycarpus	白鲜皮	Dictamnoside K	5452	NA	
D. dasycarpus	白鲜皮	Dictamnoside L	5453	NA	
D. dasycarpus	白鲜皮	Dictamnoside M	5454	NA	
D. dasycarpus	白鲜皮	Dictamnoside N	5455	NA	
D. dasycarpus	白鲜皮	Evodol	7669	NA	
D. dasycarpus	白鲜皮	Fraxinellone	7945	NA	
D. dasycarpus	白鲜皮	Isomaculosidine	11518	NA	
D. dasycarpus	白鲜皮	Kihadanin B	12226	NA	
D. dasycarpus	白鲜皮	Obacunoic acid	15883	NA	
D. dasycarpus	白鲜皮	Pregnenolone	17805	NA	
D. dasycarpus	白鲜皮	Preskimmianine	17849	NA	

D. dasycarpus	白鮮皮	Skimmianine	20002	NA	
D. dasycarpus	白鮮皮	Trigonelline	21662	NA	
D. dasycarpus	白鮮皮	γ-Fagarine	7703	NA	

Appendix 12 Biological target list for Bing pian (*Dryobalanops aromatic,* synthetic borneol)

Species	**Chinese**	**Compound**	**Compound ID**	**Target ID**	**Target name**
D. aromatica	冰片	Oleanolic acid	*16050*	T0045	Caspase-3
D. aromatica	冰片	Oleanolic acid	*16050*	T0019	Caspase-9
D. aromatica	冰片	Oleanolic acid	*16050*	T0135	Heme oxygenase 1
D. aromatica	冰片	Oleanolic acid	*16050*	T0152	Intercellular adhesion molecule 1
D. aromatica	冰片	Oleanolic acid	*16050*	T0323	NAD(P)H dehydrogenase [quinone] 1
D. aromatica	冰片	Camphor	3048	T0672	Neuronal acetylcholine receptor subunit alpha-4
D. aromatica	冰片	Oleanolic acid	*16050*	T1106	Pancreatic alpha-amylase
D. aromatica	冰片	Alphitolic acid	984	NA	
D. aromatica	冰片	Asiatic acid	1853	NA	
D. aromatica	冰片	Benzyl acetone	2274	NA	
D. aromatica	冰片	D-Borneol	2553	NA	
D. aromatica	冰片	Dipterocarpol	6502	NA	
D. aromatica	冰片	D-Isoborneol	11259	NA	
D. aromatica	冰片	Dryobalanone	6610	NA	
D. aromatica	冰片	Erythrodiol	7338	NA	
D. aromatica	冰片	L-Isoborneol	11260	NA	
D. aromatica	冰片	α-Humulene	9669	NA	
D. aromatica	冰片	β-Caryophyllene	3242	NA	
D. aromatica	冰片	β-Elemene	6741	NA	
D. aromatica	冰片	γ-Caryophyllene	3241	NA	

Appendix 13 The list of APP drug targets (from DrugBank)

App target name	Category	Action	APP drug	associated herb
6-phosphogluconate dehydrogenase, decarboxylating	Enzymes	inhibitor	Methotrexate	No
Aldehyde oxidase	Enzymes	substrate	Methotrexate	No
Aldo-keto reductase family 1 member C1	Targets	inhibitor	Salicyclic acid	Yes
ATP-binding cassette sub-family G member 2	Transporters	substrate	Methotrexate	Yes
	Transporters	inhibitor	Cyclosporine	
ATP-binding cassette transporter sub-family C member 11	Transporters	substrate	Methotrexate	No
Bifunctional purine biosynthesis protein PURH [Includes: Phosphoribosylaminoimidazolecarboxamide formyltransferase]	Enzymes	inhibitor	Methotrexate	No
Bile salt export pump	Transporters	inhibitor	Cyclosporine	No
Calcineurin subunit B isoform 2	Targets	inhibitor	Cyclosporine	No
Calcium signal-modulating cyclophilin ligand	Targets	binder	Cyclosporine	No
Canalicular multispecific organic anion transporter 1	Transporters	substrate, inhibitor	Methotrexate	No
	Transporters	inhibitor	Cyclosporine	No
Canalicular multispecific organic anion transporter 2	Transporters	substrate, inhibitor	Methotrexate	No
	Transporters	inhibitor	Cyclosporine	
Cellular retinoic acid-binding protein 1	Carriers	NS	Alitretinoin	NA
	Carriers	NS	Etretinate (w)	NA

Cellular retinoic acid-binding protein 2	Carriers	NS	Alitretinoin	NA
Complement C1q subcomponent subunit A	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Complement C1q subcomponent subunit B	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Complement C1q subcomponent subunit C	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Complement C1r subcomponent	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
	Targets	NS	Etanercept	
Corticosteroid-binding globulin	Carriers	NS	Fluticasone Propionate	NA
Corticosteroid-binding globulin	Carriers	binder	Prednisolone	No
Cytochrome P450 19A1	Enzymes	inhibitor	Etretinate (w)	No
Cytochrome P450 1A1	Enzymes	inhibitor	Clobetasol	Yes
	Enzymes	inhibitor	Methoxsalen	

Cytochrome P450 1A2	Enzymes	inhibitor	Clobetasol	Yes
	Enzymes	inhibitor	Alitretinoin	
	Enzymes	inhibitor	Methoxsalen	
Cytochrome P450 24A1, mitochondrial	Enzymes	substrate	Calcipotriol	No
	Enzymes	substrate, inducer	Calcitriol	
Cytochrome P450 26A1	Enzymes	substrate	Acitretin	No
	Enzymes	substrate	Etretinate (w)	
Cytochrome P450 2A6	Enzymes	inhibitor	Prednisolone	No
	Enzymes	inhibitor	Methoxsalen	
Cytochrome P450 2A13	Enzymes	inhibitor	Methoxsalen	No
Cytochrome P450 2C19	Enzymes	inhibitor	Cyclosporine	No
Cytochrome P450 2C8	Enzymes	substrate	Tazarotene	No
	Enzymes	inhibitor	Cyclosporine	
Cytochrome P450 2C9	Enzymes	substrate	Salicyclic acid	No
	Enzymes	inhibitor	Cyclosporine	
Cytochrome P450 2D6	Enzymes	inhibitor	Cyclosporine	No
Cytochrome P450 3A4	Enzymes	substrate, inducer	Calcitriol	Yes
	Enzymes	substrate, inhibitor	Fluticasone Propionate	
	Enzymes	substrate, inhibitor	Prednisolone	

	Enzymes	substrate, inducer	Cyclosporine	
	Enzymes	substrate	Methoxsalen	
Cytochrome P450 3A5	Enzymes	substrate, inhibitor	Fluticasone Propionate	No
	Enzymes	substrate, inducer	Cyclosporine	
Cytochrome P450 3A7	Enzymes	substrate	Fluticasone Propionate	No
	Enzymes	substrate, inducer	Cyclosporine	
Cytosolic phospholipase A2	Targets	inhibitor	Fluticasone Propionate	No
Dihydrofolate reductase	Targets	inhibitor	Methotrexate	No
Dihydrofolate reductase	Enzymes	substrate	Methotrexate	No
	Enzymes	inhibitor	Aminopterin (w)	
DNA	Targets	intercalation	Methoxsalen	No
Folylpolyglutamate synthase, mitochondrial	Enzymes	substrate	Methotrexate	No
Gamma-glutamyl hydrolase	Enzymes	substrate	Methotrexate	No
Glucocorticoid receptor	Targets	agonist	Desoximetasone	No
	Targets	agonist	Clobetasol	
	Targets	agonist	Fluticasone Propionate	
	Targets	agonist	Prednisolone	
Heme carrier protein 1	Transporters	substrate, inhibitor	Methotrexate	No
Heme carrier protein 1	Transporters	NS	Aminopterin (w)	NA

High affinity immunoglobulin gamma Fc receptor I	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Ileal sodium/bile acid cotransporter	Transporters	inhibitor	Cyclosporine	No
Integrin alpha-L	Targets	antibody	Efalizumab	No
Kelch-like ECH-associated protein 1 (KEAP1_HUMAN)	Targets	binder	Dimethyl fumarate	No
Low affinity immunoglobulin gamma Fc region receptor II-a	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Low affinity immunoglobulin gamma Fc region receptor II-b	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Low affinity immunoglobulin gamma Fc region receptor II-c	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Low affinity immunoglobulin gamma Fc region receptor III-A	Targets	NS	Etanercept	NA
	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Low affinity immunoglobulin gamma Fc region receptor III-B	Targets	NS	Etanercept	NA

	Targets	NS	Efalizumab	
	Targets	NS	Alefacept	
Lymphotoxin-alpha	Targets	NS	Etanercept	NA
Methylenetetrahydrofolate reductase	Enzymes	substrate	Methotrexate	No
Mineralocorticoid receptor	Targets	antagonist	Fluticasone Propionate	No
Monocarboxylate transporter 1	Transporters	substrate	Salicyclic acid	No
	Transporters	substrate	Methotrexate	
Multidrug resistance protein 1	Transporters	substrate	Salicyclic acid	Yes
	Transporters	substrate	Prednisolone	
	Transporters	substrate	Methotrexate	
	Transporters	substrate	Alitretinoin	
	Transporters	substrate, inhibitor, inducer	Cyclosporine	
Multidrug resistance-associated protein 1	Transporters	substrate, inhibitor	Methotrexate	No
	Transporters	inhibitor	Cyclosporine	
Multidrug resistance-associated protein 4	Transporters	substrate, inhibitor	Methotrexate	No
Multidrug resistance-associated protein 7	Transporters	inhibitor	Methotrexate	No
	Transporters	inhibitor	Cyclosporine	
Myeloperoxidase	Enzymes	inhibitor	Calcipotriol	Yes
Peptidyl-prolyl cis-trans isomerase A	Targets	NS	Cyclosporine	NA

Progesterone receptor	Targets	agonist	Fluticasone Propionate	No
Prostaglandin G/H synthase 1	Targets	inhibitor	Salicyclic acid	Yes
Prostaglandin G/H synthase 2	Targets	inhibitor	Salicyclic acid	Yes
Prostaglandin G/H synthase 2	Enzymes	inhibitor	Etanercept	
Retinoic acid receptor alpha	Targets	agonist	Tazarotene	No
	Targets	agonist	Acitretin	
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	
Retinoic acid receptor beta	Targets	agonist	Tazarotene	No
	Targets	agonist	Acitretin	
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	
Retinoic acid receptor gamma-1	Targets	agonist	Tazarotene	No
	Targets	agonist	Acitretin	
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	
Retinoic acid receptor RXR-alpha	Targets	agonist	Acitretin	No
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	

Retinoic acid receptor RXR-beta	Targets	agonist	Tazarotene	No
	Targets	agonist	Acitretin	
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	
Retinoic acid receptor RXR-gamma	Targets	agonist	Acitretin	No
	Targets	agonist	Alitretinoin	
	Targets	agonist	Etretinate (w)	
Retinol-binding protein I, cellular	Targets	agonist	Acitretin	No
Serum albumin	Carriers	other/unknown	Salicyclic acid	No
	Carriers	NS	Acitretin	NA
	Carriers	NS	Methotrexate	
Sodium/bile acid cotransporter	Transporters	inhibitor	Cyclosporine	No
Solute carrier family 22 member	Transporters	substrate	Salicyclic acid	No
Solute carrier family 22 member 10	Transporters	inhibitor	Salicyclic acid	No
Solute carrier family 22 member 11	Transporters	inhibitor	Salicyclic acid	No
	Transporters	substrate	Methotrexate	
Solute carrier family 22 member 6	Transporters	inhibitor	Salicyclic acid	No
	Transporters	substrate, inhibitor	Methotrexate	
	Transporters	inhibitor	Cyclosporine	

Solute carrier family 22 member 7	Transporters	substrate	Methotrexate	No
Solute carrier family 22 member 8	Transporters	inhibitor	Salicyclic acid	No
	Transporters	substrate, inhibitor	Methotrexate	
Solute carrier organic anion transporter family member 1A2	Transporters	inhibitor	Prednisolone	No
	Transporters	substrate	Methotrexate	
	Transporters	inhibitor	Cyclosporine	
Solute carrier organic anion transporter family member 1B1	Transporters	substrate	Methotrexate	No
	Transporters	inhibitor	Cyclosporine	
Solute carrier organic anion transporter family member 1B3	Transporters	substrate	Methotrexate	No
Solute carrier organic anion transporter family member 1C1	Transporters	substrate	Methotrexate	No
Solute carrier organic anion transporter family member 2B1	Transporters	substrate	Salicyclic acid	No
Solute carrier organic anion transporter family member 3A1	Transporters	substrate	Methotrexate	No
Solute carrier organic anion transporter family member 4C1	Transporters	NS	Methotrexate	NA
T-cell surface antigen CD2	Targets	inhibitor	Alefacept	No
Thymidylate synthase	Enzymes	substrate	Methotrexate	No
Tumor necrosis factor	Targets	antibody	golimumab	Yes
	Targets	antibody	Etanercept	
Tumor necrosis factor receptor superfamily member 1B	Targets	NS	Etanercept	NA
Vitamin D3 receptor	Targets	antagonist	Calcipotriol	No

Vitamin D3 receptor	Targets	antagonist	Calcitriol	No

(w): withdrawn by FDA; NA: not available; NS: not stated.

Appendix 14 List of Molecular Functions identified in PANTHER

Dan shen:

Molecular function	Accession	target hits
binding	(GO:0005488)	51
catalytic activity	(GO:0003824)	47
enzyme regulator activity	(GO:0030234)	17
receptor activity	(GO:0004872)	16
transcription regulator activity	(GO:0030528)	9
structural molecule activity	(GO:0005198)	6
transporter activity	(GO:0005215)	4
ion channel activity	(GO:0005216)	1
translation regulator activity	(GO:0045182)	1
antioxidant activity	(GO:0016209)	1

Xi shu:

Molecular function	Accession	target hits
binding	(GO:0005488)	75
catalytic activity	(GO:0003824)	61
transcription regulator activity	(GO:0030528)	26
receptor activity	(GO:0004872)	26
enzyme regulator activity	(GO:0030234)	15
transporter activity	(GO:0005215)	7
structural molecule activity	(GO:0005198)	6
antioxidant activity	(GO:0016209)	5
ion channel activity	(GO:0005216)	2
translation regulator activity	(GO:0045182)	1

Di huang:

Molecular function	Accession	target hits
catalytic activity	(GO:0003824)	49
binding	(GO:0005488)	44
receptor activity	(GO:0004872)	13
transcription regulator activity	(GO:0030528)	7
enzyme regulator activity	(GO:0030234)	7
transporter activity	(GO:0005215)	6
structural molecule activity	(GO:0005198)	4
antioxidant activity	(GO:0016209)	2
translation regulator activity	(GO:0045182)	1

Qing dai:

Molecular function	Accession	target hits
catalytic activity	(GO:0003824)	26
binding	(GO:0005488)	18
transcription regulator activity	(GO:0030528)	8
transporter activity	(GO:0005215)	7
receptor activity	(GO:0004872)	6
enzyme regulator activity	(GO:0030234)	3
structural molecule activity	(GO:0005198)	2
antioxidant activity	(GO:0016209)	1

Etanercept:

Molecular function	Accession	target hits
receptor activity	(GO:0004872)	8
binding	(GO:0005488)	3
structural molecule activity	(GO:0005198)	3
catalytic activity	(GO:0003824)	2

Salicylic acid:

Molecular function	Accession	target hits
transporter activity	(GO:0005215)	9
catalytic activity	(GO:0003824)	4

Appendix 15 List of Molecular Functions identified in PANTHER

Dan shen:

Biological Process	Accession	target hits
cellular process	(GO:0009987)	62
metabolic process	(GO:0008152)	59
cell communication	(GO:0007154)	50
immune system process	(GO:0002376)	36
apoptosis	(GO:0006915)	27
response to stimulus	(GO:0050896)	26
cell cycle	(GO:0007049)	25
developmental process	(GO:0032502)	22
transport	(GO:0006810)	14
system process	(GO:0003008)	14
reproduction	(GO:0000003)	9
cell adhesion	(GO:0007155)	9
cellular component organization	(GO:0016043)	6
regulation of biological process	(GO:0050789)	5
generation of precursor metabolites and energy	(GO:0006091)	5
homeostatic process	(GO:0042592)	3
localization	(GO:0051179)	2

Xi shu:

Biological Process	Accession	target hits
metabolic process	(GO:0008152)	87
cellular process	(GO:0009987)	85

cell communication	(GO:0007154)	68
immune system process	(GO:0002376)	58
response to stimulus	(GO:0050896)	48
developmental process	(GO:0032502)	33
cell cycle	(GO:0007049)	32
apoptosis	(GO:0006915)	28
reproduction	(GO:0000003)	17
system process	(GO:0003008)	13
cell adhesion	(GO:0007155)	11
transport	(GO:0006810)	10
generation of precursor metabolites and energy	(GO:0006091)	9
cellular component organization	(GO:0016043)	8
localization	(GO:0051179)	2
homeostatic process	(GO:0042592)	2

Di huang:

Biological Process	**Accession**	**target hits**
metabolic process	(GO:0008152)	56
cellular process	(GO:0009987)	53
cell communication	(GO:0007154)	48
immune system process	(GO:0002376)	44
response to stimulus	(GO:0050896)	33
apoptosis	(GO:0006915)	21
developmental process	(GO:0032502)	16
transport	(GO:0006810)	13
cell cycle	(GO:0007049)	11
system process	(GO:0003008)	9
generation of precursor metabolites and energy	(GO:0006091)	7

reproduction	(GO:0000003)	5
cellular component organization	(GO:0016043)	4
cell adhesion	(GO:0007155)	4
homeostatic process	(GO:0042592)	2
localization	(GO:0051179)	1
regulation of biological process	(GO:0050789)	1

Qing dai:

Biological Process	**Accession**	**target hits**
metabolic process	(GO:0008152)	31
cellular process	(GO:0009987)	20
immune system process	(GO:0002376)	16
cell communication	(GO:0007154)	15
apoptosis	(GO:0006915)	12
response to stimulus	(GO:0050896)	11
developmental process	(GO:0032502)	10
cell cycle	(GO:0007049)	8
system process	(GO:0003008)	6
transport	(GO:0006810)	4
reproduction	(GO:0000003)	4
cell adhesion	(GO:0007155)	3
localization	(GO:0051179)	2
cellular component organization	(GO:0016043)	2
homeostatic process	(GO:0042592)	2
generation of precursor metabolites and energy	(GO:0006091)	1

Etanercept:

Biological Process	Accession	target hits
immune system process	(GO:0002376)	13
cellular process	(GO:0009987)	12
response to stimulus	(GO:0050896)	12
developmental process	(GO:0032502)	6
cellular component organization or biogenesis	(GO:0071840)	3
apoptotic process	(GO:0006915)	3
biological adhesion	(GO:0022610)	3
metabolic process	(GO:0008152)	2
reproduction	(GO:0000003)	1
biological regulation	(GO:0065007)	1

Salicylic acid:

Biological Process	Accession	target hits
localization	(GO:0051179)	10
metabolic process	(GO:0008152)	9
cellular process	(GO:0009987)	6
multicellular organismal process	(GO:0032501)	5
immune system process	(GO:0002376)	2

Appendix 16 List of Protein Classes identified in PANTHER

Dan shen:

Protein Class	Accession	target hit
hydrolase	(PC00121)	24
enzyme modulator	(PC00095)	19
signaling molecule	(PC00207)	18
protease	(PC00190)	15
transferase	(PC00220)	15
receptor	(PC00197)	15
kinase	(PC00137)	13
extracellular matrix protein	(PC00102)	9
oxidoreductase	(PC00176)	9
transcription factor	(PC00218)	9
nucleic acid binding	(PC00171)	8
cell adhesion molecule	(PC00069)	7
calcium-binding protein	(PC00060)	7
defense/immunity protein	(PC00090)	7
transfer/carrier protein	(PC00219)	7
phosphatase	(PC00181)	5
cytoskeletal protein	(PC00085)	3
transporter	(PC00227)	3
chaperone	(PC00072)	2
surfactant	(PC00212)	2
lyase	(PC00144)	1
ligase	(PC00142)	1
structural protein	(PC00211)	1

Xi shu:

Protein Class	Accession	target hit
nucleic acid binding	(PC00171)	27
transcription factor	(PC00218)	26
signaling molecule	(PC00207)	25
receptor	(PC00197)	24
transferase	(PC00220)	20
hydrolase	(PC00121)	20
enzyme modulator	(PC00095)	18
oxidoreductase	(PC00176)	16
kinase	(PC00137)	14
protease	(PC00190)	13
extracellular matrix protein	(PC00102)	10
cell adhesion molecule	(PC00069)	7
defense/immunity protein	(PC00090)	7
transporter	(PC00227)	6
calcium-binding protein	(PC00060)	6
transfer/carrier protein	(PC00219)	5
chaperone	(PC00072)	3
phosphatase	(PC00181)	2
cell junction protein	(PC00070)	2
surfactant	(PC00212)	2
structural protein	(PC00211)	2
cytoskeletal protein	(PC00085)	1
transmembrane receptor regulatory/adaptor protein	(PC00226)	1
lyase	(PC00144)	1
ligase	(PC00142)	1
membrane traffic protein	(PC00150)	1
isomerase	(PC00135)	1

Di huang:

Protein Class	Accession	target hit
signaling molecule	(PC00207)	20
transferase	(PC00220)	17
oxidoreductase	(PC00176)	15
hydrolase	(PC00121)	13
receptor	(PC00197)	12
enzyme modulator	(PC00095)	9
nucleic acid binding	(PC00171)	8
defense/immunity protein	(PC00090)	8
transfer/carrier protein	(PC00219)	7
transcription factor	(PC00218)	7
kinase	(PC00137)	7
protease	(PC00190)	6
calcium-binding protein	(PC00060)	5
transporter	(PC00227)	4
ligase	(PC00142)	4
cytoskeletal protein	(PC00085)	3
cell adhesion molecule	(PC00069)	3
extracellular matrix protein	(PC00102)	1
lyase	(PC00144)	1
membrane traffic protein	(PC00150)	1
phosphatase	(PC00181)	1
chaperone	(PC00072)	1
surfactant	(PC00212)	1
structural protein	(PC00211)	1
isomerase	(PC00135)	1

Qing dai:

Protein Class	Accession	target hit
hydrolase	(PC00121)	13
transcription factor	(PC00218)	8
signaling molecule	(PC00207)	6
transferase	(PC00220)	5
nucleic acid binding	(PC00171)	5
receptor	(PC00197)	5
protease	(PC00190)	4
transporter	(PC00227)	4
ligase	(PC00142)	4
kinase	(PC00137)	4
oxidoreductase	(PC00176)	3
enzyme modulator	(PC00095)	3
phosphatase	(PC00181)	3
extracellular matrix protein	(PC00102)	2
cell adhesion molecule	(PC00069)	2
defense/immunity protein	(PC00090)	2
transfer/carrier protein	(PC00219)	2
surfactant	(PC00212)	2
lyase	(PC00144)	1
calcium-binding protein	(PC00060)	1

Etanercept:

Protein Class	Accession	target hit
defense/immunity protein	(PC00090)	10
receptor	(PC00197)	6

cell adhesion molecule	(PC00069)	5
extracellular matrix protein	(PC00102)	3
signaling molecule	(PC00207)	2
hydrolase	(PC00121)	1
oxidoreductase	(PC00176)	1
calcium-binding protein	(PC00060)	1
protease	(PC00190)	1

Salicylic acid:

Protein Class	**Accession**	**target hit**
transporter	(PC00227)	8
transfer/carrier protein	(PC00219)	6
oxidoreductase	(PC00176)	3

Appendix 17: List of Celluar Components identified in PANTHER

Dan shen:

Cellular component	Accession	target hit
extracellular region	(GO:0005576)	10
intracellular	(GO:0005622)	3
protein complex	(GO:0043234)	1

Xi shu:

Cellular component	Accession	target hit
extracellular region	(GO:0005576)	11
plasma membrane	(GO:0005886)	2
intracellular	(GO:0005622)	1

Di huang:

Cellular component	Accession	target hit
intracellular	(GO:0005622)	3
extracellular region	(GO:0005576)	1

Qing dai:

Cellular component	Accession	target hit
extracellular region	(GO:0005576)	2

Etanercept:

Cellular component	Accession	target hit
extracellular matrix	(GO:0031012)	3
extracellular region	(GO:0005576)	3

Salicylic acid:

Cellular component	Accession	target hit
membrane	(GO:0016020)	1

Appendix 18 List of pathways identified in PANTHER

Dan shen:

Pathway name	Acc.	No.	%T	%P
Apoptosis signaling pathway	(P00006)	22	21.80%	6.80%
Angiogenesis	(P00005)	18	17.80%	5.60%
Gonadotropin releasing hormone receptor pathway	(P06664)	17	16.80%	5.30%
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	15	14.90%	4.60%
Endothelin signaling pathway	(P00019)	12	11.90%	3.70%
Huntington disease	(P00029)	11	10.90%	3.40%
VEGF signaling pathway	(P00056)	11	10.90%	3.40%
Wnt signaling pathway	(P00057)	10	9.90%	3.10%
EGF receptor signaling pathway	(P00018)	10	9.90%	3.10%
Interleukin signaling pathway	(P00036)	9	8.90%	2.80%
FGF signaling pathway	(P00021)	9	8.90%	2.80%
B cell activation	(P00010)	9	8.90%	2.80%
Integrin signalling pathway	(P00034)	8	7.90%	2.50%
FAS signaling pathway	(P00020)	8	7.90%	2.50%
PI3 kinase pathway	(P00048)	8	7.90%	2.50%
Alzheimer disease-amyloid secretase pathway	(P00003)	7	6.90%	2.20%
Ras Pathway	(P04393)	7	6.90%	2.20%
T cell activation	(P00053)	7	6.90%	2.20%
PDGF signaling pathway	(P00047)	7	6.90%	2.20%
Alzheimer disease-presenilin pathway	(P00004)	6	5.90%	1.90%
p53 pathway	(P00059)	6	5.90%	1.90%
Toll receptor signaling pathway	(P00054)	6	5.90%	1.90%
Plasminogen activating cascade	(P00050)	6	5.90%	1.90%
Blood coagulation	(P00011)	6	5.90%	1.90%

p53 pathway feedback loops 2	(P04398)	5	5.00%	1.50%
Oxidative stress response	(P00046)	5	5.00%	1.50%
Muscarinic acetylcholine receptor 1 and 3 signaling pathway	(P00042)	5	5.00%	1.50%
5HT2 type receptor mediated signaling pathway	(P04374)	4	4.00%	1.20%
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	(P00027)	4	4.00%	1.20%
Thyrotropin-releasing hormone receptor signaling pathway	(P04394)	4	4.00%	1.20%
TGF-beta signaling pathway	(P00052)	4	4.00%	1.20%
Oxytocin receptor mediated signaling pathway	(P04391)	4	4.00%	1.20%
Histamine H1 receptor mediated signaling pathway	(P04385)	4	4.00%	1.20%
Cadherin signaling pathway	(P00012)	4	4.00%	1.20%
Interferon-gamma signaling pathway	(P00035)	3	3.00%	0.90%
Alpha adrenergic receptor signaling pathway	(P00002)	3	3.00%	0.90%
Insulin/IGF pathway-protein kinase B signaling cascade	(P00033)	3	3.00%	0.90%
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	(P00032)	3	3.00%	0.90%
Parkinson disease	(P00049)	3	3.00%	0.90%
Cytoskeletal regulation by Rho GTPase	(P00016)	3	3.00%	0.90%
Cell cycle	(P00013)	3	3.00%	0.90%
Nicotinic acetylcholine receptor signaling pathway	(P00044)	3	3.00%	0.90%
p53 pathway by glucose deprivation	(P04397)	2	2.00%	0.60%
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	(P00026)	2	2.00%	0.60%
p38 MAPK pathway	(P05918)	2	2.00%	0.60%
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	(P05911)	2	2.00%	0.60%
Axon guidance mediated by netrin	(P00009)	1	1.00%	0.30%
Axon guidance mediated by Slit/Robo	(P00008)	1	1.00%	0.30%
Beta2 adrenergic receptor signaling pathway	(P04378)	1	1.00%	0.30%
Axon guidance mediated by semaphorins	(P00007)	1	1.00%	0.30%
Beta1 adrenergic receptor signaling pathway	(P04377)	1	1.00%	0.30%
JAK/STAT signaling pathway	(P00038)	1	1.00%	0.30%
Hypoxia response via HIF activation	(P00030)	1	1.00%	0.30%
Ornithine degradation	(P02758)	1	1.00%	0.30%

Transcription regulation by bZIP transcription factor	(P00055)	1	1.00%	0.30%
P53 pathway feedback loops 1	(P04392)	1	1.00%	0.30%
Enkephalin release	(P05913)	1	1.00%	0.30%
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	(P00043)	1	1.00%	0.30%
Metabotropic glutamate receptor group I pathway	(P00041)	1	1.00%	0.30%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits (%)

Xi shu:

Pathway name	**Acc.**	**No.**	**%T**	**%P**
Gonadotropin releasing hormone receptor pathway	(P06664)	22	16.40%	7.10%
Angiogenesis	(P00005)	20	14.90%	6.40%
Apoptosis signaling pathway	(P00006)	18	13.40%	5.80%
Interleukin signaling pathway	(P00036)	18	13.40%	5.80%
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	16	11.90%	5.10%
p53 pathway	(P00059)	13	9.70%	4.20%
VEGF signaling pathway	(P00056)	11	8.20%	3.50%
EGF receptor signaling pathway	(P00018)	10	7.50%	3.20%
PDGF signaling pathway	(P00047)	10	7.50%	3.20%
PI3 kinase pathway	(P00048)	9	6.70%	2.90%
p53 pathway feedback loops 2	(P04398)	8	6.00%	2.60%
Wnt signaling pathway	(P00057)	8	6.00%	2.60%
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	(P00032)	7	5.20%	2.30%
Huntington disease	(P00029)	7	5.20%	2.30%
Ras Pathway	(P04393)	7	5.20%	2.30%
T cell activation	(P00053)	7	5.20%	2.30%
Endothelin signaling pathway	(P00019)	7	5.20%	2.30%
B cell activation	(P00010)	7	5.20%	2.30%

Toll receptor signaling pathway	(P00054)	6	4.50%	1.90%
FGF signaling pathway	(P00021)	6	4.50%	1.90%
FAS signaling pathway	(P00020)	6	4.50%	1.90%
Integrin signalling pathway	(P00034)	5	3.70%	1.60%
Insulin/IGF pathway-protein kinase B signaling cascade	(P00033)	5	3.70%	1.60%
Plasminogen activating cascade	(P00050)	5	3.70%	1.60%
Oxidative stress response	(P00046)	5	3.70%	1.60%
Blood coagulation	(P00011)	5	3.70%	1.60%
Alzheimer disease-presenilin pathway	(P00004)	4	3.00%	1.30%
Cell cycle	(P00013)	4	3.00%	1.30%
Cadherin signaling pathway	(P00012)	4	3.00%	1.30%
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	(P05911)	4	3.00%	1.30%
Alzheimer disease-amyloid secretase pathway	(P00003)	3	2.20%	1.00%
Interferon-gamma signaling pathway	(P00035)	3	2.20%	1.00%
Hypoxia response via HIF activation	(P00030)	3	2.20%	1.00%
TGF-beta signaling pathway	(P00052)	3	2.20%	1.00%
Parkinson disease	(P00049)	3	2.20%	1.00%
5HT2 type receptor mediated signaling pathway	(P04374)	2	1.50%	0.60%
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	(P00027)	2	1.50%	0.60%
p53 pathway by glucose deprivation	(P04397)	2	1.50%	0.60%
Thyrotropin-releasing hormone receptor signaling pathway	(P04394)	2	1.50%	0.60%
Oxytocin receptor mediated signaling pathway	(P04391)	2	1.50%	0.60%
p38 MAPK pathway	(P05918)	2	1.50%	0.60%
DNA replication	(P00017)	2	1.50%	0.60%
Histamine H1 receptor mediated signaling pathway	(P04385)	2	1.50%	0.60%
Muscarinic acetylcholine receptor 1 and 3 signaling pathway	(P00042)	2	1.50%	0.60%
JAK/STAT signaling pathway	(P00038)	1	0.70%	0.30%
Purine metabolism	(P02769)	1	0.70%	0.30%
Alpha adrenergic receptor signaling pathway	(P00002)	1	0.70%	0.30%
Pentose phosphate pathway	(P02762)	1	0.70%	0.30%

Ubiquitin proteasome pathway	(P00060)	1	0.70%	0.30%
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	(P00026)	1	0.70%	0.30%
Vitamin D metabolism and pathway	(P04396)	1	0.70%	0.30%
Ornithine degradation	(P02758)	1	0.70%	0.30%
Hedgehog signaling pathway	(P00025)	1	0.70%	0.30%
Glycolysis	(P00024)	1	0.70%	0.30%
Adenine and hypoxanthine salvage pathway	(P02723)	1	0.70%	0.30%
P53 pathway feedback loops 1	(P04392)	1	0.70%	0.30%
Fructose galactose metabolism	(P02744)	1	0.70%	0.30%
Metabotropic glutamate receptor group I pathway	(P00041)	1	0.70%	0.30%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits (%)

Di huang:

Pathway name	**Acc.**	**No.**	**%T**	**%P**
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	18	19.40%	7.40%
Apoptosis signaling pathway	(P00006)	15	16.10%	6.20%
Gonadotropin releasing hormone receptor pathway	(P06664)	15	16.10%	6.20%
Interleukin signaling pathway	(P00036)	13	14.00%	5.30%
Angiogenesis	(P00005)	11	11.80%	4.50%
T cell activation	(P00053)	11	11.80%	4.50%
B cell activation	(P00010)	9	9.70%	3.70%
Huntington disease	(P00029)	8	8.60%	3.30%
VEGF signaling pathway	(P00056)	7	7.50%	2.90%
Toll receptor signaling pathway	(P00054)	7	7.50%	2.90%
Endothelin signaling pathway	(P00019)	7	7.50%	2.90%
EGF receptor signaling pathway	(P00018)	7	7.50%	2.90%
Ras Pathway	(P04393)	6	6.50%	2.50%

FGF signaling pathway	(P00021)	6	6.50%	2.50%
FAS signaling pathway	(P00020)	6	6.50%	2.50%
PI3 kinase pathway	(P00048)	6	6.50%	2.50%
p53 pathway	(P00059)	5	5.40%	2.10%
Wnt signaling pathway	(P00057)	5	5.40%	2.10%
PDGF signaling pathway	(P00047)	5	5.40%	2.10%
Alzheimer disease-amyloid secretase pathway	(P00003)	4	4.30%	1.60%
Integrin signalling pathway	(P00034)	4	4.30%	1.60%
p53 pathway feedback loops 2	(P04398)	4	4.30%	1.60%
TGF-beta signaling pathway	(P00052)	4	4.30%	1.60%
Oxidative stress response	(P00046)	4	4.30%	1.60%
Muscarinic acetylcholine receptor 1 and 3 signaling pathway	(P00042)	4	4.30%	1.60%
Interferon-gamma signaling pathway	(P00035)	3	3.20%	1.20%
Insulin/IGF pathway-protein kinase B signaling cascade	(P00033)	3	3.20%	1.20%
Hypoxia response via HIF activation	(P00030)	3	3.20%	1.20%
Parkinson disease	(P00049)	3	3.20%	1.20%
Axon guidance mediated by netrin	(P00009)	2	2.20%	0.80%
5HT2 type receptor mediated signaling pathway	(P04374)	2	2.20%	0.80%
Alpha adrenergic receptor signaling pathway	(P00002)	2	2.20%	0.80%
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	(P00032)	2	2.20%	0.80%
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	(P00027)	2	2.20%	0.80%
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	(P00026)	2	2.20%	0.80%
Thyrotropin-releasing hormone receptor signaling pathway	(P04394)	2	2.20%	0.80%
Oxytocin receptor mediated signaling pathway	(P04391)	2	2.20%	0.80%
Histamine H1 receptor mediated signaling pathway	(P04385)	2	2.20%	0.80%
Nicotinic acetylcholine receptor signaling pathway	(P00044)	2	2.20%	0.80%
Blood coagulation	(P00011)	2	2.20%	0.80%
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	(P00043)	2	2.20%	0.80%
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	(P05911)	2	2.20%	0.80%
Axon guidance mediated by Slit/Robo	(P00008)	1	1.10%	0.40%

Axon guidance mediated by semaphorins	(P00007)	1	1.10%	0.40%
JAK/STAT signaling pathway	(P00038)	1	1.10%	0.40%
Purine metabolism	(P02769)	1	1.10%	0.40%
p53 pathway by glucose deprivation	(P04397)	1	1.10%	0.40%
Ornithine degradation	(P02758)	1	1.10%	0.40%
Hedgehog signaling pathway	(P00025)	1	1.10%	0.40%
Transcription regulation by bZIP transcription factor	(P00055)	1	1.10%	0.40%
Adenine and hypoxanthine salvage pathway	(P02723)	1	1.10%	0.40%
p38 MAPK pathway	(P05918)	1	1.10%	0.40%
Cytoskeletal regulation by Rho GTPase	(P00016)	1	1.10%	0.40%
Nicotine degradation	(P05914)	1	1.10%	0.40%
Cell cycle	(P00013)	1	1.10%	0.40%
Metabotropic glutamate receptor group I pathway	(P00041)	1	1.10%	0.40%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits (%)

Qing dai:

Pathway name	**Acc.**	**No.**	**%T**	**%P**
Apoptosis signaling pathway	(P00006)	11	25.60%	9.80%
Angiogenesis	(P00005)	7	16.30%	6.30%
Gonadotropin releasing hormone receptor pathway	(P06664)	7	16.30%	6.30%
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	5	11.60%	4.50%
Huntington disease	(P00029)	5	11.60%	4.50%
PDGF signaling pathway	(P00047)	5	11.60%	4.50%
Interleukin signaling pathway	(P00036)	4	9.30%	3.60%
FAS signaling pathway	(P00020)	4	9.30%	3.60%
Integrin signalling pathway	(P00034)	3	7.00%	2.70%
Wnt signaling pathway	(P00057)	3	7.00%	2.70%

VEGF signaling pathway	(P00056)	3	7.00%	2.70%
Ras Pathway	(P04393)	3	7.00%	2.70%
T cell activation	(P00053)	3	7.00%	2.70%
PI3 kinase pathway	(P00048)	3	7.00%	2.70%
B cell activation	(P00010)	3	7.00%	2.70%
Alzheimer disease-amyloid secretase pathway	(P00003)	2	4.70%	1.80%
Interferon-gamma signaling pathway	(P00035)	2	4.70%	1.80%
Insulin/IGF pathway-protein kinase B signaling cascade	(P00033)	2	4.70%	1.80%
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade	(P00032)	2	4.70%	1.80%
p53 pathway	(P00059)	2	4.70%	1.80%
Toll receptor signaling pathway	(P00054)	2	4.70%	1.80%
FGF signaling pathway	(P00021)	2	4.70%	1.80%
TGF-beta signaling pathway	(P00052)	2	4.70%	1.80%
Endothelin signaling pathway	(P00019)	2	4.70%	1.80%
EGF receptor signaling pathway	(P00018)	2	4.70%	1.80%
Oxidative stress response	(P00046)	2	4.70%	1.80%
Angiotensin II-stimulated signaling through G proteins and beta-arrestin	(P05911)	2	4.70%	1.80%
Alzheimer disease-presenilin pathway	(P00004)	1	2.30%	0.90%
5HT2 type receptor mediated signaling pathway	(P04374)	1	2.30%	0.90%
Alpha adrenergic receptor signaling pathway	(P00002)	1	2.30%	0.90%
Hypoxia response via HIF activation	(P00030)	1	2.30%	0.90%
Pentose phosphate pathway	(P02762)	1	2.30%	0.90%
p53 pathway feedback loops 2	(P04398)	1	2.30%	0.90%
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	(P00027)	1	2.30%	0.90%
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	(P00026)	1	2.30%	0.90%
Hedgehog signaling pathway	(P00025)	1	2.30%	0.90%
Glycolysis	(P00024)	1	2.30%	0.90%
Thyrotropin-releasing hormone receptor signaling pathway	(P04394)	1	2.30%	0.90%
Oxytocin receptor mediated signaling pathway	(P04391)	1	2.30%	0.90%
Parkinson disease	(P00049)	1	2.30%	0.90%

Histamine H1 receptor mediated signaling pathway	(P04385)	1	2.30%	0.90%
Heme biosynthesis	(P02746)	1	2.30%	0.90%
Glutamine glutamate conversion	(P02745)	1	2.30%	0.90%
Cadherin signaling pathway	(P00012)	1	2.30%	0.90%
Fructose galactose metabolism	(P02744)	1	2.30%	0.90%
Muscarinic acetylcholine receptor 1 and 3 signaling pathway	(P00042)	1	2.30%	0.90%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits (%)

Etanercept:

Pathway name	Acc.	No.	%T	%P
Apoptosis signaling pathway	(P00006)	3	23.10%	42.90%
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	1	7.70%	14.30%
Wnt signaling pathway	(P00057)	1	7.70%	14.30%
Endothelin signaling pathway	(P00019)	1	7.70%	14.30%
Toll receptor signaling pathway	(P00054)	1	7.70%	14.30%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits (%)

Salicylic acid:

Pathway name	Acc.	No.	%T	%P
Inflammation mediated by chemokine and cytokine signaling pathway	(P00031)	2	15.40%	50.00%
Endothelin signaling pathway	(P00019)	1	7.70%	25.00%
Toll receptor signaling pathway	(P00054)	1	7.70%	25.00%

Acc. Accession No in PANTHER; No.: Number of target hits in the pathway; %T: target hits/total no. targets (%);%P: target hits/total no. pathway hits

Appendix 19. List of protein targets in the top 5 pathways identified in PANTHER

Target name	Panther name	Ang	Int	Inf	Gon	Apo	HIT name
12-LO	Arachidonate 12-lipoxygenase, leukocyte-type				1		NA
3' FSHbeta	Follitropin subunit beta				1		Follitropin subunit beta
3' LHbeta	Luteinizing hormone beta				1		Lutropin subunit beta
5' FSHbeta	5-hydroxytryptamine receptor 3A				1		5-hydroxytryptamine receptor 3A
5' LHbeta	5' LHbeta				1		NA
5-HT3AR	5-HT3AR				1		NA
A1	Bcl2-related protein A1					1	Bcl-2-related protein A1
AC	Adenylate cyclase			1	1		Adenylate cyclase type 2, 8, 10
ActRII	Activin receptor type-2A				1		NA
ActRII/IIB	Activin receptor type-2A/2B				1		NA
Adiponectin	Adiponectin				1		Adiponectin
AdipoR1/R2	Adiponectin receptor protein 1/2				1		Adiponectin receptor protein 1/2
AIF	Apoptosis inducing factor					1	NA
AK006051	AK006051				1		NA
AKT	RAC-alpha serine/threonine-protein kinase	1		1	1	1	RAC-alpha serine/threonine-protein kinase
Alk4	Activin type I receptor				1		NA
alpha-beta integrin dimer	Integrin alpha/beta-1				1		Integrin beta-1
AMPK	5'-AMP-activated protein kinase subunit alpha-1/beta-1/beta-2/gamma-1/gamma-2; 45 kDa calcium-binding protein				1		5'-AMP-activated protein kinase subunit gamma-2
Ang-1	Angiopoietin-1	1					Angiopoietin-1
Ang-2	Angiopoietin-2	1					NA

Annexin A5	Annexin A5				1		Annexin A5
AP-1	activator protein-1			1			Transcription factor AP-1
Apaf-1	Apoptosis protease activating factor-1					1	Apoptotic protease-activating factor 1
APC	Adenomatous Polyposis of the Colon	1					Adenomatous polyposis coli protein
AR	Androgen receptor				1		Androgen receptor
Arp2/3	Actin related protein 2/3 complex			1			NA
ASK1	Apoptosis signal-regulating kinase-1					1	Mitogen-activated protein kinase kinase kinase 5
ATF	Activating transcription factor					1	Cyclic AMP-dependent transcription factor ATF
ATF2	ATF2				1		NA
Atf3	Cyclic AMP-dependent transcription factor ATF-3				1		NA
Axin	Axis inhibitor 1	1					NA
BAD	Bcl2 antagonist of cell death	1	1			1	Bcl2 antagonist of cell death
Bag	Bcl-2 associated anthogene-1					1	BAG family molecular chaperone regulator 3
Bak	Bcl-2 antogonist/killer					1	Bcl-2 homologous antagonist/killer
Bax	Bcl-2 associated x protein					1	Apoptosis regulator BAX
Bcl-2	Bcl-2					1	Apoptosis regulator Bcl-2
Bcl-w	Bcl-w					1	Bcl-2-like protein 2
Bcl-xL	Bcl2-related protein long isoform					1	Bcl-2-like protein 1
Bcl-xS	Bcl2-related protein short isoform					1	Bcl-2-like protein 1
beta catenin	Beta-catenin (beta catenin)	1					Catenin beta-1
beta-arrestin	Beta-arrestin			1			Beta-arrestin
Bi1	Bax inhibitor-1					1	NA
Bid	BH-3 interacting domain death agonist					1	BH3-interacting domain death agonist
Bik	Bcl-2 interacting killer					1	Bcl-2-interacting killer

Bim	Bim					1	Bcl-2-like protein 11
Blk	Bcl-2 interacting killer					1	NA
BMP2/4/15	Bone morphogenetic protein 2/4/15				1		Bone morphogenetic protein 2/4
BMP6/7	Bone morphogenetic protein 6/7				1		NA
BMP7	Bone morphogenetic protein 7				1		NA
BMPR-IA/IB/II	Bone morphogenetic protein receptor type-1A/1B/2				1		Bone morphogenetic protein receptor type-2
Bok	Bcl-2 related ovarian killer					1	Bcl-2-related ovarian killer protein
Ca/CaMK II	Calcium/calmodulin-dependent protein kinase type II subunit beta				1		NA
Caln	Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform				1		Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform
CaMK	Calcium/calModulin-dependent Kinase II, Calcium /calmodulin-dependent protein kinase kinase 2			1			Calcium/calmodulin-dependent protein kinase kinase 2
Caspase 10	Caspase 10					1	Caspase-10
Caspase 3	Caspase 3					1	Caspase-3
Caspase 7	Caspase 7					1	Caspase-7
Caspase 8	Caspase 8					1	Caspase-8
Caspase 9	Caspase 9	1				1	Caspase-9
Caveolin-1	Caveolin-1				1		Caveolin-1
CBP	CREB-binding protein				1		NA
Cdc42	Cell division cycle 42 (Cdc42), related to PAK, Cell division control protein 42 homolog			1	1		Cell division control protein 42 homolog
c-fos	c-Fos Transcription Factor (c-Fos)	1	1		1		Proto-oncogene c-Fos
CGA	Glycoprotein hormones alpha chain				1		NA
CHK	Chemokine (CHK)			1			C-C motif chemokine, C-X-C motif chemokine
CHKR	Chemokine receptor (CHKR)			1			C-C chemokine receptor
c-IAP1,2	Cellular inhibitor of apoptosis protein 1 and					1	Baculoviral IAP repeat-containing protein 3

	2 (c-IAP1,2)						
c-Jun	c-Jun Transcription Factor (c-Jun), member of the AP-1 (activator protein-1) family	1				1	Transcription factor AP-1
CLIM2	LIM domain-binding protein 1				1		NA
c-Myc	Myc proto-oncogene protein		1				Myc proto-oncogene protein
CNP	C-type natriuretic peptide				1		C-type natriuretic peptide
COX2	Prostaglandin G/H synthase 2				1		Prostaglandin G/H synthase 2
cPLA2	Cytosolic Phospholipase A2	1					Cytosolic Phospholipase A2
c-Raf	RAF proto-oncogene serine/threonine-protein kinase				1		RAF proto-oncogene serine/threonine-protein kinase
CREB	Cyclic AMP-responsive element-binding protein 1				1		Cyclic AMP-responsive element-binding protein 1
Crk	Crk oncogene	1					NA
Csda	DNA-binding protein A				1		NA
CSL	CBF1, Suppressor of Hairless, Lag-1 Transcription Factor Family (CSL)	1					NA
CTMP	C-terminal modulator protein		1				NA
CTNNB1	Catenin beta-1				1		Catenin beta-1
Cyclooxygenase	Cyclooxygenase, COX			1			Prostaglandin G/H synthase
Cytochrome C	Cytochrome C					1	Cytochrome c
Cytokine receptor	Cytokine receptor			1			NA
DAXX	Death-associated protein 6					1	Death domain-associated protein 6
Delta/Serrate	Delta	1					NA
DGK-zeta	Diacylglycerol kinase zeta				1		Diacylglycerol kinase theta
Diva	Diva					1	Bcl-2-like protein 10
Dnm1	Dynamin-1				1		NA
Dok-R	Docking Protein-R	1					Docking protein 2

DRD2	D(2) dopamine receptor				1		D(2) dopamine receptor
Dsh	Dishelvelled	1					NA
ds-RNA	ds-RNA					1	NA
DUSP1	Dual specificity protein phosphatase 1				1		Dual specificity protein phosphatase 1
ECM	ECM				1		NA
EGF	Pro-epidermal growth factor				1		Pro-epidermal growth factor
EGFR	Epidermal growth factor receptor				1		Epidermal growth factor receptor
EGR1	Early growth response protein 1				1		Early growth response protein 1
EIF2A	Eukaryotic translation initiation factor 2A				1		Eukaryotic translation initiation factor 2 subunit 1/ alpha
EIF2AK3	Eukaryotic translation initiation factor 2-alpha kinase 3				1		NA
ELF2alpha	Translation initiation factor 2-alpha					1	Eukaryotic translation initiation factor 2 subunit 1
ELK	NS		1				ETS domain-containing protein Elk-1
ELK1	ETS domain-containing protein Elk-1				1		ETS domain-containing protein Elk-1
EMC	ExtraCellular matrix protein			1			Collagen alpha
endoG	Endonuclease G					1	NA
eNOS	endothelial nitric oxide synthase	1	1				Nitric oxide synthase, endothelial
Eph	Ephrin	1					NA
EphR	Ephrin Receptor	1					Ephrin type-B receptor 2, Ephrin type-A receptor 2
ER	Steroid hormone receptor ERR1				1		Steroid hormone receptor ERR1
ERK	Extracellular signal-regulated kinase family	1	1				Mitogen-activated protein kinase 1, 3,7,12
ERK1/2	Mitogen-activated protein kinase 1/3				1		Mitogen-activated protein kinase 1/3
Ets	v-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 1 (Ets)	1	1				Protein C-ets-1
F-actin	F-actin			1			Actin, cytoplasmic 1, Alpha-actinin-1, F-actin

							cross-linking protein
FADD	Fas associated death domain					1	NA
FAK	Focal Adhesion Kinase	1			1		Focal adhesion kinase 1
FAS	FAS					1	Tumor necrosis factor receptor superfamily member 6
FAS ligand	FAS ligand					1	Tumor necrosis factor ligand superfamily member 6
FGF	Fibroblast Growth Factor	1					Fibroblast Growth Factor
FGFR-1	Fibroblast Growth Factor Receptor-1	1					Fibroblast Growth Factor Receptor 1
FKHRL1	Forkhead in Rhabdomyosarcoma-like 1		1				NA
Flip	FLICE inhibitory protein					1	CASP8 and FADD-like apoptosis regulator
Follistatin	Follistatin				1		NA
Fos	Proto-oncogene c-Fos				1	1	Proto-oncogene c-Fos
Fosb	Protein fosB				1		Protein fosB
FRP	Frizzled-Related Protein	1					NA
FRS-2	Fibroblast Growth Factor Receptor Substrate 2	1					NA
FSHbeta	Follitropin subunit beta				1		Follitropin subunit beta
FVIIa	Factor VIIa	1					Coagulation factor VII
Fzd	Frizzled	1					NA
Galphai	Gi-protein, alpha subunit			1			Guanine nucleotide-binding protein G(i) subunit alpha-1
Galphai/q	Gi/q-protein, alpha subunit			1			Guanine nucleotide-binding protein G(i) subunit alpha
Galphaq	Gq-protein, alpha subunit			1			NA
GAP	GTPase-Activating Protein	1					Ras GTPase-activating protein 1
GATA2/4	Endothelial transcription factor GATA-2/4				1		Endothelial transcription factor GATA-2
Gbeta	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1 /2/3; Guanine nucleotide-binding protein subunit beta-4 /5				1		NA

Gbetagamma	G protein, beta and gamma subunit			1			Guanine nucleotide-binding protein G(s) subunit beta
GC	Guanylate cyclase soluble subunit beta-1; Protein Gucy1b2				1		Guanylate cyclase soluble subunit beta-1
GCK	Germinal center kinase					1	Mitogen-activated protein kinase kinase kinase kinase 2
GCKR	Germinal center kinase related					1	Mitogen-activated protein kinase kinase kinase kinase 4, Mitogen-activated protein kinase kinase kinase kinase 3
GEF	Guanine nucleotide exchange factor			1			Guanine nucleotide exchange factor GEFT
Ggamma	Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-2				1		NA
Glut1	Solute carrier family 2, facilitated glucose transporter member 1				1		Solute carrier family 2, facilitated glucose transporter member 1
gnai	Guanine nucleotide-binding protein G(i) subunit alpha-1/2; Guanine nucleotide-binding protein G(k) subunit alpha				1		Guanine nucleotide-binding protein G(i) subunit alpha-1; Guanine nucleotide-binding protein G(k) subunit alpha
gnai/o	Guanine nucleotide-binding protein G(o) subunit alpha; Guanine nucleotide-binding protein G(i) subunit alpha-1				1		NA
gnaq/11	Guanine nucleotide-binding protein subunit alpha-11; Guanine nucleotide-binding protein G(q) subunit alpha				1		NA
gnas	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas				1		NA
GnRH	Progonadoliberin-1				1		Progonadoliberin-1
GnRHR	Gonadotropin-releasing hormone receptor				1		Gonadotropin-releasing hormone receptor
GPR147/74	GPR147/74				1		NA
GPRK	G-protein receptor kinase, G protein-coupled receptor kinases			1			NA
GR	Glucocorticoid receptor				1		Glucocorticoid receptor
Granzyme B	Granzyme B					1	Granzyme B
Grb	Growth factor receptor-bound protein			1			NA
Grb14	Growth Factor Receptor-Bound Protein 14	1					NA
Grb2	Growth factor receptor-bound protein 2	1	1		1		NA

Grb7	Growth Factor Receptor-Bound Protein 7	1					NA
GSK3	Glycogen synthase kinase-3 beta		1		1		Glycogen synthase kinase-3
GSK3beta	Glycogen synthase kinase 3-beta	1					Glycogen synthase kinase-3 beta
GTPase	Rho guanosine triphosphatase	1					NA
HIF-1	Hypoxia Inducible Factor-1	1					Hypoxia-inducible factor 1-alpha
HSP27	Heat-Shock Protein 27	1					Heat shock protein beta-1
HSP70	Heat shock protein 70					1	Heat shock 70 kDa protein 1A/1B
Id2	DNA-binding protein inhibitor ID-2				1		NA
Id3	DNA-binding protein inhibitor ID-3				1		NA
IGF-1	Insulin-like growth factor I				1		Insulin-like growth factor IA
IGF-1R	Tyrosine-protein kinase receptor				1		NA
IGFR2	Insulin-like growth factor II receptor					1	Insulin-like growth factor II receptor
IkappaB	Inhibitor of kappa light chain gene enhancer in B cells			1		1	NF-kappa-B inhibitor alpha
Ikk	Inhibitor of kappa-B kinase		1	1		1	Inhibitor of nuclear factor kappa-B kinase subunit alpha/beta
IL2	Interleukin-2			1			Interleukin-2
INFgamma	Interferon gamma			1			Interferon gamma
Inha	Inha				1		NA
Inhba	Inhba				1		NA
Inhba/b	Inhba/b				1		NA
Insulin	Insulin				1		Insulin; Insulin B chain; Insulin A chain
Integrin	Integrin beta-3			1			Integrin beta-3
Interleukin	Interleukins		1				Interleukin-XX
IP3R	Inositol 1,4,5-triphosphate receptor			1	1		Inositol 1,4,5-trisphosphate receptor type 1

IR	Insulin receptor				1		Insulin receptor
IRS	Insulin receptor substrate				1		Insulin receptor substrate 1
IRS-1	Insulin receptor substrate 1				1		Insulin receptor substrate 1
IRS1/2	Insulin receptor substrate family		1				Insulin receptor substrate
Isl-1	Insulin gene enhancer protein ISL-1				1		NA
JAK	Janus kinase, Tyrosine-protein kinase JAK1		1	1			Tyrosine-protein kinase JAK1
JAK1	Janus Kinase 1	1			1		Tyrosine-protein kinase JAK1; Janus kinase 1
JNK	Jun kinase (JNK), c-Jun NH(2)-terminal kinase					1	Mitogen-activated protein kinase 8, 9, 10
JNK1	c-Jun N-Terminal Kinase 1	1					Mitogen-activated protein kinase 8
JNK1/2	Mitogen-activated protein kinase 1/2				1		Mitogen-activated protein kinase 1
JNKK1	c-Jun N-terminal Kinase Kinase 1	1					Dual specificity mitogen-activated protein kinase kinase 4
JUN	Transcription factor AP-1; Transcription factor jun-B				1		Transcription factor AP-1; Transcription factor jun-B
Junc	Transcription factor AP-1				1		Transcription factor AP-1
Jund	Transcription factor jun-D				1		Transcription factor jun-D
KSR-1	Kinase suppressor of Ras 1				1		NA
Lepr	Lepr				1		Leptin receptor
Leptin	Leptin				1		Leptin; Obesity factor
LHbeta	Luteinizing hormone beta				1		Lutropin subunit beta; Lutropin beta chain; Luteinizing hormone subunit beta
LHX2	LIM/homeobox protein Lhx2				1		NA
Lipoxygenase	Lipoxygenase			1			Arachidonate 5-lipoxygenase
L-type Ca2+	Voltage-dependent L-type calcium channel subunit alpha-1S/1C/1D; L-type dihydropyridine-sensitive calcium channel alpha-1f subunit				1		Voltage-dependent L-type calcium channel subunit alpha-1C
MADD	Mitogen activated protein kinase activating death domain					1	MAP kinase-activating death domain protein

MAP2K1/2	Dual specificity mitogen-activated protein kinase kinase 1/2				1		Dual specificity mitogen-activated protein kinase kinase 1
MAP3Ks	Mitogen-activated protein kinase kinase kinase 1-14				1		Mitogen-activated protein kinase kinase kinase 1/4/5
MAP4Ks	Mitogen-activated protein kinase kinase kinase kinase 1-5				1		Mitogen-activated protein kinase kinase kinase kinase 4
MAPK	Mitogen activated protein kinase [1-7, 11 and higher]			1		1	Mitogen-activated protein kinase 1, 3, 5, 7, 8, 10, 12, 13
MAPKAPK2	Mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2)		1				NA
MAPKAPK2/3	Mitogen-activated protein kinase-activated protein kinase 2 and 3 (MAPKAPK2/3)	1					NA
MASH1	Achaete-scute homolog 1				1		NA
Mcl1	Myeloid cell leukemia 1					1	Induced myeloid leukemia cell differentiation protein Mcl-1
MEK	Mitogen-activated protein kinase kinase	1	1	1			Dual specificity mitogen-activated protein kinase kinase
MEK1/2	Dual specificity mitogen-activated protein kinase kinase 1/2				1		Dual specificity mitogen-activated protein kinase kinase 1
MEKK1	Mitogen-activated protein kinase kinase kinase 1	1				1	Mitogen-activated protein kinase kinase kinase 1
miR-132/212	Heat shock 70 kDa protein 1A				1		Heat shock 70 kDa protein 1A/1B
MIS	Anti-Mullerian hormone				1		NA
MISRII	Anti-Muellerian hormone type-2 receptor				1		NA
MKK3	Mitogen activated protein kinase kinase 3					1	Dual specificity mitogen-activated protein kinase kinase 3
MKK3/6	Dual specificity mitogen-activated protein kinase kinase 3/6				1		NA
MKK4/7	Dual specificity mitogen-activated protein kinase kinase 4/7				1		Dual specificity mitogen-activated protein kinase kinase 4/7
MKK7	Mitogen activated protein kinase kinase 7					1	Dual specificity mitogen-activated protein kinase kinase 7
MLCK	Myosin light chain kinase			1			NA
MNK1/2	Mitogen-activated protein kinase-interacting serine/threonine kinase1/2		1				NA
mPer1	Period circadian protein homolog 1				1		Period circadian protein homolog 1
MT1-MMP	Matrix metalloproteinase-14				1		Matrix metalloproteinase-14

mTOR	mammalian target of rapamycin		1				Serine/threonine-protein kinase mTOR
Myosin	Myosin			1			Myosin-7
NAB	NGFI-A-binding protein 1/2				1		NA
Nck	Nck Adaptor Protein	1					NA
Ncoa3	Nuclear receptor coactivator 3				1		NA
NFAT	Nuclear factor of activated T-cells			1	1		Nuclear factor of activated T-cells 5
NFkappaB	Nuclear factor kappa-B			1		1	Transcription factor p65, Nuclear factor NF-kappa-B p105 subunit
NF-Y	Nuclear transcription factor Y subunit alpha/beta/gamma				1		NA
NIK	NF kappa B inducing kinase					1	Mitogen-activated protein kinase kinase kinase kinase 4
NOSI	Inhibition of nitric oxide type I				1		NA
Notch	Notch Receptor	1					Neurogenic locus notch homolog protein 1
nPKCs	Protein kinase C epsilon/delta type				1		Protein kinase C epsilon/delta type
Npr2	Atrial natriuretic peptide receptor 2				1		NA
Nur77	Nuclear receptor subfamily 4 group A member 1				1		Nuclear receptor subfamily 4 group A member 1
OCT-1	POU domain, class 2, transcription factor 1				1		POU domain, class 2, transcription factor 1
OTX	Homeobox protein OTX1				1		NA
p21CIP1	Cyclin-dependent kinase inhibitor 1A		1				Cyclin-dependent kinase inhibitor 1
p27KIP1	Cyclin-dependent kinase inhibitor 1B		1				Cyclin-dependent kinase inhibitor 1B
p300	Histone acetyltransferase p300				1		Histone acetyltransferase p300
p38	Activator of 90 kDa heat shock protein ATPase homolog 1				1		Activator of 90 kDa heat shock protein ATPase homolog 1
p38MAPK	p38 Mitogen-Activated Protein Kinase	1					NA
p53	Tumor protein p53					1	Cellular tumor antigen p53
p65	NFkappaB				1		Transcription factor p65; Nuclear factor NF-kappa-B p65 subunit

p90RSK	Ribosomal protein S6 kinase, 90kD (p90RSK)		1				Ribosomal protein S6 kinase alpha-1
PAC1R	Pituitary adenylate cyclase-activating polypeptide type I receptor				1		NA
PAC1-R	Pituitary adenylate cyclase-activating polypeptide type I receptor				1		NA
PACAP	Pituitary adenylate cyclase-activating polypeptide				1		Pituitary adenylate cyclase-activating polypeptide
PACT	Protein activator of interon-induced protein kinase					1	NA
PAK	P21-activated kinase	1		1			Serine/threonine-protein kinase PAK
PAR	Protease Activated Receptor	1					Proteinase-activated receptor 2
Paxillin	Paxillin	1			1		NA
Pbx1	Pre-B-cell leukemia transcription factor 1				1		NA
Pcaf	Histone acetyltransferase KAT2B				1		NA
PDGF	Platelet-Derived Growth Factor	1					Platelet-derived growth factor subunit A, Platelet-derived growth factor subunit B
PDGFR	Platelet-Derived Growth Factor Receptor	1					Beta-type platelet-derived growth factor receptor
PDK1	3-phosphoinositide-dependent protein kinase 1; Phosphoinositide-dependent kinase-1, 3-phosphoinositide-dependent protein kinase 1			1			NA
PDK1/2	3-phosphoinositide-dependent protein kinase 1 and 2		1				NA
PEA-15	Astrocytic phosphoprotein PEA-15				1		NA
PG Rcs	Prostacyclin receptor;Prostaglandin E2 receptor EP1/2/4 subtype; Prostaglandin E receptor 3 (Subtype EP3), isoform CRA_a; Prostaglandin F2-alpha receptor				1		Prostacyclin receptor;Prostaglandin E2 receptor EP2 subtype; Prostaglandin E receptor 3 (Subtype EP3), isoform CRA_a; Prostaglandin F2-alpha receptor
PI3K	Phosphatidylinositol 3-kinase	1	1	1	1	1	Phosphatidylinositol 3-kinase regulatory subunit alpha
PITX	Pituitary homeobox 1/2				1		NA
PKA	Protein kinase A, cAMP-dependent protein kinase			1	1		NA
PKB	Protein kinase B		1				RAC-alpha serine/threonine-protein kinase

PKC	Protein kinase C , All types	1		1			Protein kinase C alpha type, Protein kinase C beta type
PKCe/theta	Protein kinase C epsilon/theta type				1		Protein kinase C epsilon/zeta type
PKCs	Protein kinase C; Protein kinase C beta/detla/epsilon/zeta type				1	1	Protein kinase C; Protein kinase C beta/detla/epsilon/zeta type
PKCs(3)	Protein kinase C; Protein kinase C detla/epsilon type				1		Protein kinase C alpha/beta/detla/epsilon/gamma type
PKCzeta	Protein kinase C, zeta			1			Protein kinase C zeta type
PKR	Interferon-inducible double-stranded RNA-activated protein kinase (PKR)					1	NA
PLA2	Phospholipase A2	1		1	1		Cytosolic phospholipase A2
PLCbeta	phosphodiesterase beta				1		1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-1/2
PLCbetagamma	Phospholipase C , 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-2			1			1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-2, 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1
PLC-gamma	Phospholipase C-gamma	1					1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1
PLD	Phospholipase D	1			1		Phosphatidylinositol-glycan-specific phospholipase D
PPARalpha/gamma	Peroxisome proliferator-activated receptor alpha/gamma				1		Peroxisome proliferator-activated receptor alpha/gamma
PPARgamma	Peroxisome proliferator-activated receptor gamma				1		Peroxisome proliferator-activated receptor gamma
PR	Progesterone receptor				1		Progesterone receptor
Prep1	protein PKNOX1				1		NA
PRLR	Prolactin receptor				1		NA
Pro-inflammatory anti-apoptotic genes	Pro-inflammatory genes			1			NA
Pro-inflammatory genes	Pro-inflammatory genes			1			NA
Prolactin	Prolactin				1		Prolactin
Prx2	paired related homeobox 2				1		NA

PTEN	Phosphatase and tensin homologue			1			Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN
PYK2	Proline-rich tyrosine kinase 2, Protein-tyrosine kinase 2-beta			1	1		Protein-tyrosine kinase 2-beta
Rac	Ras-related C3 botulinum toxin substrate	1		1			Ras-related C3 botulinum toxin substrate 1
Rac1	Ras-related C3 botulinum toxin substrate 1				1		Ras-related C3 botulinum toxin substrate 1
Raf	Raf Oncogene	1	1				RAF proto-oncogene serine/threonine-protein kinase
Raf-1	RAF proto-oncogene serine/threonine-protein kinase			1			RAF proto-oncogene serine/threonine-protein kinase
RAIDD	RIP associated ICH-1/CED homologous protein with death domain					1	NA
Rap1b	Ras-related protein Rap-1b				1		NA
Ras	Rat Sarcoma GTP-binding protein	1	1	1	1		NA
RasGAP	Ras GTPase-Activating Protein	1	1				Ras GTPase-activating protein 1
Receptor subunit alpha	Interleukin receptor alpha subunit		1				Interleukin-2 receptor subunit alpha
Receptor subunit beta	Interleukin receptor beta subunit (Receptor subunit beta)		1				Interleukin-2 receptor subunit beta
RFRP-1/-3	RFamideRelated Peptide-1/-3				1		NA
RGS	Regulator of G-protein signaling			1			Regulator of G-protein signaling
Rho	Rho			1			Transforming protein RhoA
RICS	Rho GTPase-activating protein 32				1		NA
RIP	Receptor interacting protein (RIP)					1	NA
ROCK	Rho-associated coiled-coil Ser/Thr specific kinase (ROCK)			1			NA
Runx2	Runt-related transcription factor 2				1		Runt-related transcription factor 2
Scg2	Secretogranin-2				1		NA
Sck	Shc-like protein	1					NA
SEK1	SAPK/ERK kinasae 1					1	Dual specificity mitogen-activated protein kinase kinase 4

SF1	Steroidogenic factor 1				1		NA
Shc	SH2 homology domain containing transforming protein	1	1	1			NA
SHIP	SH2 domain-containing inositol 5-phosphatase			1			Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2
SHP2	Src homology 2 domain-containing tyrosine phosphatase 2	1					NA
Signaling subunit	NS		1				Interleukin-6 receptor subunit beta
SKIL	Ski-like protein				1		NA
Smac/Diablo	Second mitochondria-derived activator of caspase					1	NA
SMAD1/5/8	Mothers against decapentaplegic homolog 1/5/9				1		Mothers against decapentaplegic homolog 1
SMAD2-4	Mothers against decapentaplegic homolog 2-4				1		Mothers against decapentaplegic homolog 2-3
SN	SN				1		NA
SNURF	Small nuclear ribonucleoprotein-associated protein N upstream reading frame protein				1		NA
SOCS	Suppressor of cytokine siganling			1			Suppressor of cytokine signaling 7
SODD	Silencer of death domains					1	BAG family molecular chaperone regulator 3
SOS	Son of sevenless		1	1	1		NA
SOS-1	Son of Sevenless, Drosophila, Homolog 1	1					NA
SP1	Transcription factor Sp1				1		Transcription factor Sp1
SP3	Transcription factor Sp3				1		NA
SPK	Sphingosine Kinase	1					Sphingosine kinase 1
Src	Src tyrosine kinase	1			1		Proto-oncogene tyrosine-protein kinase Src
Src-like	Src-like-adapter 2		1				NA
SrcPTK	Src family tyrosine kinase			1			NA
SRF	Serum response factor		1		1		NA

STAT	Signal transducer and activator of transcription		1	1			Signal transducer and activator of transcription
STAT1	Signal transducer and activator of transcription 1	1					Signal transducer and activator of transcription 1-alpha/beta
STAT3	Signal transducer and activator of transcription 3	1			1		Signal transducer and activator of transcription 3
Survivin	Baculoviral IAP Repeat-Containing Protein 5	1					Baculoviral IAP repeat-containing protein 5
Syt IV	Synaptotagmin-4				1		NA
TAK1, MAP3K7	Mitogen-activated protein kinase kinase kinase 7				1		NA
TBRIII	Transforming growth factor beta receptor type 3				1		NA
TCF	T-Cell Transcription Factor	1			1		Transcription factor 7
TF	Tissue Factor	1					Tissue Factor
TGFbeta	Transforming growth factor beta				1		Transforming growth factor beta
TGIF1	Homeobox protein TGIF1				1		NA
Tie2	Tie-2	1					NA
TNF	Tumor necrosis factor					1	Tumor necrosis factor
TNFR1	Tumor necrosis factor receptor 1					1	Tumor necrosis factor receptor superfamily member 1B
TNFR2	Tumor necrosis factor receptor 2					1	Tumor necrosis factor receptor superfamily member 1A
TORC1	transcription coactivator 1				1		NA
TRADD	TNFR1 associated death domain					1	NA
TRAF2	TNF receptor-associated factor 2					1	TNF receptor-associated factor 2 (TRAF2)
TRAIL	TNF-related apoptosis inducing ligand					1	Tumor necrosis factor ligand superfamily member 10
TRAIL-R	TRAIL-receptor					1	Tumor necrosis factor receptor superfamily member 10
Tubulin	Tubulin				1		Tubulin alpha-1A chain
Unknown GPCR	Unknown G protein-coupled receptor				1		NA
VEGF	Vascular Endothelial Growth Factor	1					Vascular Endothelial Growth Factor A, Vascular Endothelial Growth Factor B

VEGFR-2	Vascular Endothelial Growth Factor Receptor-2	1					Vascular endothelial growth factor receptor 2
VE-PTP	Vascular Endothelial Protein Tyrosine Phosphatase	1					NA
Vinculin	Vinculin				1		NA
VRAP	VEGFR-Associated Protein	1					NA
Wnt	Wingless-type MMTV integration site family member	1					NA
XIAP	X-linked inhibitor of apoptosis					1	Baculoviral IAP repeat-containing protein 4
Zeb1	Zinc finger E-box-binding homeobox 1				1		NA

1: Yes; Ang.: Angiogenesis pathway; Int.: Interleukin signaling pathway; Inf.: Inflammation mediated by chemokine and cytokine signaling pathway; Gon.: Gonadotropin releasing hormone receptor pathway; Apo.: Apoptosis pathway

Appendix 20 Target name in chapter 7 and the corresponding full name in chapter 8

Abbreviation	Full name in Ch7	Full name in Ch8
AIF	Apoptosis-inducing factor	NS
bak	Bcl-2 antogonist/killer	NS
Bax	Bcl-2-associated x protein	Apoptosis regulator BAX
bcl	B-cell lymphoma 2 family of apoptosis regulator proteins	Apoptosis regulator Bcl-2
CASP1	Caspase-1	Caspase-1
CASP3	Caspase-3	Caspase-3
CASP7	Caspase-7	Caspase-7
CASP8	Caspase-8	Caspase-8
CASP9	Caspase-9	Caspase-9
CAT	Catalase	Catalase
CD14	Cluster of differentiation 14	NS
CDKs	Cyclin-dependent kinases	NS
CHK	Cultured human keratinocytes	C-C motif chemokine
COX-1	Cyclooxygenase-1	Prostaglandin G/H synthase 1
COX-2	Cyclooxygenase-2	Prostaglandin G/H synthase 2
ER	Estrogen receptor	NS
ERK	Extracellular signal-regulated kinase family	Mitogen-activated protein kinase
GSH	Intracellular glutathione	NS
GSH-Px	glutathione peroxidase	NS
GSK 3β	phosphorylation of glycogen synthase kinase 3β	Glycogen synthase kinase-3 beta
IFN-γ	Interferon-gamma	Interferon gamma
IgE	Immunoglobulin E	NS
IgG2a	Immunoglobulin G2a	NS
IKK	IκBα kinase	Inhibitor of nuclear factor kappa-B kinase subunit alpha/beta
IL- 31	Interleukin 31	NS

IL-10	Interleukin 10	Interleukin 10
IL-17	Interleukin 17	NS
IL-1β	Interleukin 1beta	Interleukin 1
IL-22	Interleukin 22	NS
IL-4	Interleukin 4	Interleukin 4
IL-5	Interleukin 5	NS
IL-6	Interleukin 6	Interleukin 6
IL-8	Interleukin 8	Interleukin 8
iNOS	Inducible nitric oxide Synthase	Nitric oxide synthase, inducible
IP-10	Interferon gamma-induced protein 10	C-X-C motif chemokine 10
IκB-α	IkappaB kinase	NF-kappa-B inhibitor alpha
JNKs	c-Jun N-terminal kinase	Mitogen-activated protein kinase
MCP-1	Monocyte chemotactic protein-1	C-C motif chemokine 2
mRNA	messenger RNA	messenger RNA
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells	Transcription factor p65
NF-κB p65	Transcription factor p65	Transcription factor p65
NIK	NF-κB-inducing kinase	Mitogen-activated protein kinase kinase kinase kinase 4
NK-1R	Neurokinin-1 receptor	NS
NO	Nitrogen oxide	NS
OMPs	Outer-membrane proteins	NS
p21	Cyclin-dependent kinase inhibitor 1	Cyclin-dependent kinase inhibitor 1
p38	Activator of 90 kDa heat shock protein ATPase homolog 1	Activator of 90 kDa heat shock protein ATPase homolog 1
p53	Cellular tumor antigen	Cellular tumor antigen p53
PARP	Poly (ADP-ribose) polymerase	Poly [ADP-ribose] polymerase 4
pCDK2	Phospho-Cyclin-dependent kinase 2	NS
PCNA	Proliferating Cell Nuclear Antigen	Proliferating Cell Nuclear Antigen
PGE2	Prostaglandin E2	Prostaglandin E2

PPAR-α	Peroxisome proliferator-activated receptor	Peroxisome proliferator-activated receptors
PU.1	Transcription factor PU.1	NS
RAGE	Receptor for advanced glycation end products	NS
RIP2	Receptor interacting protein-2	NS
RSK2	Ribosomal S6 kinase 2 kinase	NS
SOD	Superoxide dismutase	Superoxide dismutase
TARC/CCL17	Thymus and activation regulated chemokine	NS
TLR 4	Toll-like receptor 4	Toll-like receptor 4
TNF-α	Tumour necrosis factor-alpha	Tumour necrosis factor-alpha
α-SMA	α-smooth muscle actin	NS

NS: Not stated.