Chinese Herbal Medicine for Chronic Urticaria and Psoriasis Vulgaris: Clinical Evidence and Patient Experience

A thesis submitted in fulfilment of the requirement for the 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 qualify 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

Thesis related:

1. **Yu JJ**, Zhang CS, Coyle ME, Du Y, Zhang AL, Guo X, Xue CC, Lu C*. Compound glycyrrhizin plus conventional therapy for psoriasis vulgaris: a systematic review and meta-analysis of randomized controlled trials. Current Medical Research and Opinion. 2017;33:279-87. (Journal article)
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Abbreviations

AD	Anno Domini
ADR	Adverse drug reactions
AE	Adverse event
AMED	Allied and Complementary Medicine Database
BC	Before Christ
CAM	Complementary and alternative medicines
CBM	China BioMedical Literature
CCTs	Controlled clinical trials
CD	Compact disc
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Compound Glycyrrhizin
CHM	Chinese herbal medicine
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CI	Confidence interval
CM	Chinese medicine
CNKI	China National Knowledge Infrastructure
COX-2	Cyclooxygenase-2
CQVIP	Chongqing VIP
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
DPU	Delayed pressure urticaria
Embase	Excepta Medica Database
ER	Effective rate
HLA	Human leukocyte antigen
HR-QoL	Health-related quality of life

IgE	Immunoglobulin type E
IL-12	Interleukin-12
IL-17	Interleukin-17
IL-22	Interleukin-22
IL-23	Interleukin-23
IL-6	Interleukin-6
iNOS	Inducible NO synthase
ITT	Intention-to-treat
IV	Intravenous
LPS	Lipopolysaccharide
MAPKs	Mitogen activated protein kinases
MD	Mean difference
MTX	Methotrexate
NB-UVB	Narrow-band ultraviolet B
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
PAF	Platelet-activating factor
PASI	Psoriasis Area Severity Index
PGE2	Prostaglandin E_2
PICF	Patient informed consent form
PROSPERO	An international database of prospectively registered systematic reviews
PsA	Psoriatic arthritis
PSORS1	Psoriasis susceptibility 1
PUVA	Psoralen and ultraviolet A
QoL	Quality of life
RCTs	Randomised controlled trials

RD	Risk difference
RR	Risk ratio
SR	Systematic review
SSRI	Symptom Severity Reduction Index
TAFE	Training and further education
Th1	Type 1 helper T cell
Th17	Type 17 helper T cell
TNF	Tumour necrosis factor
UAS	Urticaria Activity Score
UCT	Urticaria Control Test
USS	Urticaria Severity Score
US	United States
UV-A	Ultraviolet A
UV-B	Ultraviolet B
WM	Western medicine
ZHYD	*Zhong Hua Yi Dian*
11β -OHSD	11β-hydroxysteroid dehydrogenase

Summary

Background

Urticaria and psoriasis are two of the most common chronic skin disorders that have a great impact on patients' quality of life. Western medicine (WM) provides short-term symptomatic relief. However, a long-term strategy for managing refractory urticaria is lacking and unwanted side effects have been associated with long-term use of such therapies for psoriasis.

In WM, chronic urticaria and psoriasis vulgaris are attributed to immune dysfunction (as the underlying internal factor) and are triggered by external factors. In Chinese medicine (CM), these two conditions share the same pathogenesis of an underlying deficiency of healthy, protective *qi* with an external pathogenic factor.

In terms of treatment principle, the concept of using the same treatment for different diseases (异病同治) is very common in CM clinical practice. This is defined as applying the same treatment method to patients who suffer from different disease but have the same patterns. As both conditions result from immune dysfunction in WM, and share the same treatment principle from a CM perspective, the clinical management of these two conditions was evaluated to explore the current state of clinical evidence of Chinese herbal medicine (CHM).

To provide the best available evidence on the efficacy and safety of CHM for both conditions, 'whole evidence' from both classical literature and clinical studies was evaluated systematically. Pre-clinical evidence was briefly summarised to explain potential mechanisms of CHM. In addition, practicability, such as patients' experiences of using CHM, should be considered when CHM is considered as part of clinical practice.

Objectives

The objectives of this study are to:

1. evaluate the evidence of CHM for chronic urticaria and psoriasis vulgaris in the classical CM literature
2. evaluate the current clinical trial evidence of CHM for chronic urticaria
3. evaluate the current clinical trial evidence of compound glycyrrhizin (CG) (extract from Chinese herb *gan cao* 甘草, radix *glycyrrhizae*) for psoriasis vulgaris
4. summarise the current experimental evidence of CHM for chronic urticaria and psoriasis vulgaris
5. explore patients' experiences of using CHM for the treatment of chronic urticaria and psoriasis vulgaris.

Methods

Evidence Evaluation of CHM in Classical Literature

Classical literature research was conducted based on the *Zhong Hua Yi Dian*. Citations related to chronic urticaria and psoriasis vulgaris were found by searching the *Zhong Hua Yi Dian*. Descriptive analysis was performed to calculate the frequency of formulae and herbs used in the *Zhong Hua Yi Dian* citations likely to involve chronic urticaria and psoriasis vulgaris.

Evidence Evaluation of Chinese Herbal Medicine in Clinical Trials

Clinical evidence was evaluated and synthesised through systematic reviews (SRs) of randomised controlled trials (RCTs). All SRs were conducted following the rigorous

methodology of the Cochrane Collaboration. In addition, experimental evidence from modern literature was also summarised and incorporated into the SRs.

Experiences of using Chinese Herbal Medicine

A qualitative description method was used to explore patients' experiences living with these two conditions and using CHM. Data were collected through individual semi-structured interviews.

Results

Evidence from Classical Literature

The findings indicate that *Xiao feng san* 消风散 is the most commonly reported formula for urticaria in the classical literature, and is still used in current clinical practice. For psoriasis vulgaris, the most frequently reported formula is *Sou feng shun qi wan* 搜风顺气丸, which differs from contemporary practice. The CHM treatments for these two conditions have several herbs in common, including *fang feng* 防风, *jing jie* 荆芥, *gan cao* 甘草, *qiang huo* 羌活, *dang gui* 当归 and *chuan xiong* 川芎.

Evidence from Clinical Trials

Two SRs on CHM for chronic urticaria included 100 RCTs (10,258 participants). The results suggested that CHM alone (RR: 1.21 [1.15, 1.29], I^2=0%) or as an add-on therapy to second-generation antihistamines (RR: 1.19 [1.10, 1.27], I^2 = 54%) improved symptoms of chronic urticaria by 30% or more when compared with second-generation antihistamines. CHM was well tolerated by patients with chronic urticaria. Methodological flaws of the included studies and uncertain validity of outcomes limited the certainty of the findings. The key herbs used in

the formulae for chronic urticaria in included studies appeared to have anti-inflammatory, anti-allergenic and antipruritic actions.

The third SR focused on the add-on effect of CG to conventional therapy for psoriasis vulgaris. Eleven RCTs (1,200 participnats) were included in this SR. CG plus conventional therapy enhanced clinical response in terms of psoriasis area severity index (PASI) 60 (RR: 1.30 [1.21, 1.40], I^2 = 6%) and90 (RR: 1.37 [1.21, 1.56], I^2 = 0%), and did not increase the frequency of adverse events for patients with psoriasis vulgaris. However, the findings should be interpreted with caution due to methodological flaws in the included studies. The long-term add-on effect was uncertain. CG was considered to have an anti-inflammatory and immune-modulating effect based on experimental evidence.

Experience of using Chinese Herbal Medicine

The findings suggested that patients living with psoriasis vulgaris or chronic urticaria were burdened by physical and psychological effects. Long-term use of conventional treatments resulted in unpleasant side effects, which undermined participants' confidence in conventional treatments. Based on participants' own beliefs and experiences, they sought CHM as treatment. Most participants experienced satisfactory responses to CHM, but some found it hard to manage.

Conclusions

Evidence from classical literature showed the most frequently used formulae and herbs for both conditions in ancient times, which could guide contemporary clinical practice and drug discovery. SRs of clinical evidence produced through this research suggested that CHM was well tolerated and had promising benefits in improving clinical outcomes. These provided the evidence of efficacy and safety necessary for clinical decision-making, CM education and

further research. A general summary of pharmacological action of key herbs indicated that the herbs possessed anti-inflammatory, anti-allergenic, antipruritic and immune-modulating actions. When choosing CHM, patients expected accessible treatments which could reduce relapse rates with no side effects. Understanding patients' expectations and experiences is helpful when communicating with patients about their therapeutic options. Further, it provides direction for future research.

Chapter 1. Introduction

1.1 Introduction

Chronic urticaria and psoriasis vulgaris are two common chronic and recurrent skin conditions, which have similar prevalence in the global population (1–9). The pathogenesis of both conditions is related to immune dysfunction and is triggered by external factors (10–13). In addition to the considerable health-related (physical and psychological) burdens these conditions inflict on patients, both chronic urticaria and psoriasis vulgaris place significant economic burdens on individuals and healthcare systems (13–22).

For both conditions, Western medicine (WM) can provide rapid relief of symptoms. However, long-term use of WM remains a challenge due to uncomfortable side effects and a lack of treatment response from some patients (10, 12, 13, 23). Patients may look to complementary and alternative medicines (CAM) when WM treatment does not meet their expectations. Studies show the use of CAM, including herbal medicine for skin conditions, is increasing (24–26).

Chronic urticaria and psoriasis vulgaris are two examples of dermatological diseases with similarities in WM pathogenesis and Chinese herbal medicine (CHM) management. One Chinese medicine (CM) treatment principle can be applied to both conditions, that is to deal with presenting symptoms during the acute phase of the condition, and address the root cause (underlying internal factors) during the chronic phase of the condition. Treatment must address both symptoms and root causes but be guided by the primary cause of the condition (急则治其标, 缓则治其本, 标本兼治, 治病必求于本).

Moreover, the concept of using the same treatment for different diseases (异病同治) is very common in CM clinical practice. This is defined as applying the same treatment method to patients who suffer from different disease that have the same patterns. As both conditions result from immune dysfunction in WM, and share the same treatment principle from a CM perspective, it is valuable to explore the current state of clinical evidence of Chinese herbal medicine (CHM).

CM has a long history in treating dermatological diseases. CM classical literature contains an abundance of information on CHM for chronic urticaria and psoriasis vulgaris in ancient times. Many of the formulae described in contemporary textbooks and guidelines have their origins in classical literature. However, classical literature has not been evaluated using a systematic approach. Meanwhile, evidence from clinical trials of CHM for chronic urticaria and psoriasis vulgaris is increasing. Synthesis of information from classical literature and clinical trials is lacking. A 'whole evidence' approach was used in this project, which was to search, evaluate and systematically analyse evidence from classical literature and modern literature. This included randomised controlled trials (RCTs), non-randomised controlled trials and non-controlled studies. This comprehensive approach can identify potential therapies for further evaluation and guide clinical practice.

1.2 Rationale of the Research

This project addresses several gaps in the understanding of CHM use for chronic urticaria and psoriasis vulgaris. The classical literature includes discussions of CM concepts in texts, dating back to the Spring and Autumn periods (770–476 BC) (27). Books are written in Chinese. Many texts do not have an English translation and hard copies may be difficult to obtain. The *Zhong Hua Yi Dian* (*ZHYD*) provides a digitalised and searchable collection of more than 1,100 books. This project provides a summary of the information from classical

literature. Many of these sources would not otherwise be accessible to people who do not read Chinese.

Further, systematic reviews (SRs) of clinical evidence provide the best available indication of efficacy and safety for clinical decision-making, CM education and further research. For psoriasis vulgaris, several SRs have evaluated the efficacy and safety of CHM (28–31). Reviews have focused on evaluation of CHM as an intervention. No reviews that examined the efficacy of a particular herb, formula or product were identified. For example, a CHM product called compound glycyrrhizin (CG), with its key constituent glycyrrhizin extracted from *gan cao* 甘草, is commonly used in clinical practice in China for psoriasis vulgaris. No reviews published in English have evaluated the efficacy of this compound. For chronic urticaria, two SRs have focused on a particular formula (*Dang gui yin zi* 当归饮子) (32, 33) and the third review evaluated CHM but with a narrow scope (34). To address these gaps, this project will undertake additional evaluation to provide a more comprehensive evaluation of best available evidence for treatment of these two conditions.

Through previously published SRs of psoriasis vulgaris, the researcher identified key herbs that may be promising for both conditions. To examine the pharmacological actions of the key herbs used in the SRs, the researcher reviewed a selection of experimental studies that reported actions relevant to chronic urticaria and psoriasis vulgaris. This could inform drug discovery research and ensure the most relevant active compounds are extracted for CHM preparation.

Most studies focus on the efficacy and safety of CHM for the conditions. However, little attention has been paid to the end-users, including patients. A qualitative study was conducted to explore the use of CHM for chronic urticaria and psoriasis vulgaris. The qualitative study highlighted the motivators for people to use CHM and their experiences of

using CHM to manage their skin condition. The findings from this component of the project will help inform CM clinical practice and contribute valuable information for future research study design.

Finally, the project integrated the classical literature with current clinical practice guidelines, clinical evidence and patients' experiences. This information can guide contemporary practice and clinical research.

1.3 Aim

This project aims to evaluate the efficacy and safety of CHM for chronic urticaria and psoriasis vulgaris. Further, it aims to explore patients' experiences of using CHM for the treatment of these two conditions.

1.4 Research Questions

1. What is the understanding of CHM for chronic urticaria and psoriasis vulgaris in the classical CM literature?
2. What is the current clinical trial evidence of CHM for chronic urticaria?
3. What is the current clinical trial evidence of compound glycyrrhizin (extract from Chinese herb *gan cao* 甘草, radix *glycyrrhizae*) for psoriasis vulgaris?
4. What is the current experimental evidence of CHM for chronic urticaria and psoriasis vulgaris?
5. What are patients' experiences using CHM for the treatment of chronic urticaria or psoriasis vulgaris?

1.5 Organisation of the Thesis

This thesis includes 10 chapters. Chapter 1 introduces the research background of this project. The rationale and aim of the research are highlighted. The research questions are included and an overview of the thesis is presented.

Chapter 2 describes the understanding of chronic urticaria and psoriasis vulgaris from a WM perspective, including the definition, epidemiology, aetiology, pathophysiology, diagnosis and classification/subtypes. Current conventional management and its limitations are also identified and reviewed.

Chapter 3 describes the understanding of chronic urticaria and psoriasis vulgaris from a CM perspective through a general review of contemporary clinical guidelines and key textbooks. The contents include the terminology, aetiology, pathophysiology, syndrome differentiation, treatment principles, CHM treatments (oral and topical), acupuncture and other therapies.

Chapter 4 evaluates the evidence of CHM for both conditions in over 1,100 classical literature books contained in a compact disc (CD) version of *ZHYD* (*Encyclopaedia of traditional Chinese medicine*). The classical literature research procedure for both conditions is described in detail. *ZHYD* citations related to urticaria and psoriasis vulgaris are identified. The frequently used formulae and herbs are calculated through descriptive analysis.

Chapter 5 describes the general methodology used to evaluate the clinical evidence. All SRs follow the procedure suggested by *Cochrane handbook for systematic reviews of interventions* (89).

Chapter 6 and Chapter 7 are two SRs on CHM for chronic urticaria. Chapter 6 evaluates the efficacy and safety of CHM alone for chronic urticaria when compared with second-generation antihistamines. Chapter 7 evaluates the efficacy and safety of CHM add-on

therapy to second-generation antihistamines. Further, the main pharmacological actions of the key formulae and herbs are summarised in these two chapters. Chapter 8 systematically evaluates the clinical evidence on the add-on effect of CG to conventional therapy for psoriasis vulgaris and its safety.

Chapter 9 presents a qualitative study, which explores the patients' experiences of living with chronic urticaria and psoriasis vulgaris and using CHM to manage the conditions. The research method and findings are described in this chapter.

Chapter 10 summarises and discusses the research findings, similarities and differences across chapters, and limitations of this project. Implications for clinical practice and further research are also highlighted. This chapter also includes conclusions drawn from this research.

Chapter 2. Chronic Urticaria and Psoriasis Vulgaris in Western Medicine

2.1 Definition of Chronic Urticaria and Psoriasis Vulgaris

Urticaria and psoriasis are two common skin disorders. The typical characteristic of urticaria is the development of wheals (also called hives), either alone or accompanied by angioedema (10). The feature of wheals is a central swelling area, which is surrounded by erythema and usually accompanied by pruritus (itching) and/or a burning sensation (10). Wheals vary in size from a few millimetres to several centimetres (35). They develop quickly and usually resolve within 24 hours. In contrast, angioedema may present with erythematous or skin-coloured swelling of the lower dermis and subcutis, with pain rather than pruritus (10). Angioedema can take up to 72 hours to resolve (10). Wheals may develop in response to a stimulus (induced urticaria) or there may be no identifiable trigger (spontaneous urticaria).

Depending on duration of the condition, urticaria is classified as acute or chronic (10). Acute urticaria is defined as the spontaneous onset of wheals and/or oedema that lasts less than six weeks (10). Chronic urticaria refers to the occurrence of symptoms lasting for six or more weeks and is categorised as either spontaneous (chronic spontaneous urticaria) or inducible (10). Symptoms can occur daily or almost daily (36), or at irregular intervals (37). In clinical appearance, chronic urticaria is not different from acute urticaria (37).

Psoriasis is a chronic, genetic, systemic and inflammatory disorder that can be influenced by environmental factors (13). It may have potential associations with other inflammatory disorders or metabolic syndromes, such as psoriatic arthritis or diabetes (12, 13). Psoriasis vulgaris is the most common type of psoriasis, observed in approximately 80–90% of patients (13). Psoriasis vulgaris appears as sharply marginated, erythematous patches or plaques with

a characteristic silvery-white micaceous scale. The plaques are round or oval and are typically located on the scalp, trunk, buttocks and limbs, especially on extensor surfaces of the elbows and knees (13). Psoriasis vulgaris may progress to other types of psoriasis, such as erythrodermic or pustular types, due to inappropriate therapies or infection (12, 13).

2.2 Epidemiology of Chronic Urticaria and Psoriasis Vulgaris

2.2.1 Prevalence of Chronic Urticaria and Psoriasis Vulgaris

The prevalence of various types of urticaria ranges from 0.5% (8) to 8.8% (9). For psoriasis, it ranges from 0.47% (2) to 8.5% (1–7). According to the National Hospital Morbidity Database from the Australian Institute of Health and Welfare, urticaria hospitalisation rates increased from 5.6 in 1993–1994 to 10.3 in 2004–2005 (per 100,000 people), with an average annual increase of 5.7% (38). In China, the prevalence of urticaria is unknown. The prevalence of psoriasis in Victoria (Australia) is 6.6% (6), while in China it is 0.47% (2). Prevalence of psoriasis vulgaris is higher in young females than males (1); for chronic urticaria, prevalence is higher in females overall, regardless of age (9, 37).

Prevalence of psoriasis vulgaris is also influenced by geographical location (for example, cooler climate [39] and ethnicity [4]). It appears that variables, including physical environment, genetic factors and behavioural patterns, play a role in the progression of psoriasis (39).

2.2.2 Impact of Chronic Urticaria and Psoriasis Vulgaris on Health-related Quality of Life

The impact of chronic urticaria on quality of life (QoL) has been rated as comparable to that of coronary artery disease (17). Functional limitation has been reported in mobility, pain, energy, sleep, and mood changes including depression, life stress, social interaction and emotional reactions (14–17). Patients were not always aware of the level of limitation

experienced due to urticaria (14). The prevalence of psychosocial factors in people with chronic spontaneous urticaria was estimated to be 46.09% in an SR conducted in Canada (40).

Although psoriasis is not life threatening, research has linked it to an increased risk of cardiovascular disease, diabetes and cancer, among other morbidities (13). In addition to the burden of symptoms such as scaling, itching and skin redness, the amount of time required to treat extensive skin or scalp lesions and to maintain clothing and bedding also adversely affects QoL. Psychological wellbeing can be affected, including lowered self-esteem, anxiety, sexual dysfunction and depression (18, 19). Suicide may occur if the illness is severe (18, 19). Patients with psoriasis suffer physical and mental disabilities that are comparable to (or greater than) those found in patients with other chronic diseases, such as tumour, arthritis, hypertension, cardiovascular disease and diabetes (41).

2.2.3 Economic Burden of Chronic Urticaria and Psoriasis Vulgaris

Medication costs accounted for nearly two thirds (US$1,280) of the total annual direct cost of US$2,047 per patient (20) for chronic spontaneous urticaria. This is likely to be an underestimation because factors such as waiting time and costs accrued by carers and family were not considered. The direct average annual costs of mild psoriasis vulgaris per patient ranged from €500 to €2,000, and for severe disease from €4,000 to €10,000 in Germany (21, 22). Indirect costs, including work absenteeism, early retirement and unemployment due to psoriasis, added a further €1,600 on average (22).

2.2.4 Similarities in Chronic Urticaria and Psoriasis Vulgaris

The prevalence of chronic urticaria and psoriasis vulgaris is similar (0.5–8.8% v. 0.47–8.5%) (1–7). Both conditions have a significant impact on patients' QoL, including physical and

psychological influences. The economic burden of chronic urticaria and psoriasis vulgaris is high in both direct and indirect costs.

2.3 Aetiology and Pathophysiology of Chronic Urticaria and Psoriasis Vulgaris

2.3.1 Risk Factors

Chronic urticaria is more commonly observed in women than men (9, 37). For around one to two per cent of patients, symptoms of chronic urticaria seem to be caused by ingestion or contact with certain substances (such as food, medication and cosmetics etc.), infection, hormonal changes or systemic disease (42). A food must be ingested regularly to cause chronic urticaria (42). In endemic regions, multicellular parasites may cause chronic urticaria as they can trigger strong immunoglobulin type E (IgE) response (42). In rare cases, menses has been reported to cause or worsen chronic urticaria symptoms (42). The occurrence of chronic urticaria can be associated with rheumatic or other autoimmune diseases (42).

A risk factor of psoriasis is possibly genetics because most patients have a family history (39). Obesity does not appear to be a factor that triggers the onset of psoriasis, but patients with psoriasis tend to be overweight. In contrast, smoking is more likely to play a role in the onset of psoriasis (43), while alcohol can influence the progression of the disease (44). Stress is another important trigger factor of psoriasis and may influence the development of the condition (45). Apart from the internal factors, some medications may be associated with the onset or exacerbation of psoriasis, including anti-malarial drugs, nonsteroidal anti-inflammatory drugs, β-blockers, lithium salts and the withdrawal of steroids (46). Acute infections, mainly bacterial (streptococcal), may trigger or exacerbate psoriasis, especially guttate-type psoriasis (46). Conversely, the consumption of fruit and vegetables, carrots, tomatoes or other foods containing β-carotene can decrease the risk of psoriasis (47).

2.3.2 Pathophysiological Process of Chronic Urticaria and Psoriasis Vulgaris

The pathophysiology of urticaria is complicated. According to conventional medical knowledge, urticaria is considered a mast cell driven disease (10, 11). Although the trigger and signals of mast cell activation remain unknown, inflammatory cytokines, histamine, platelet-activating factor (PAF) and other mediators have been shown to be released from activated dermal mast cells (10). This process may lead to sensory nerve activation, vasodilation and extravasation of fluid and cell recruitment to urticarial lesions (10, 11).

Between 30 and 50% of chronic urticaria can be attributed to autoimmune disease based on the most accepted hypothesis (11, 48). Chronic urticaria has been associated with other autoimmune diseases, such as systemic lupus erythematosus, Still disease and Sjögren syndrome (8). Thyroid antibody levels are higher in patients with chronic urticaria (48). In autoimmune-origin urticaria, IgE receptors or IgE bound to receptors are activated by histamine-releasing auto-antibodies, which can stimulate the degranulation of mast cells and basophils (49).

Pruritus observed in the clinical manifestation of urticaria is caused by the rapid release of histamine, which induces the vasodilatation and extravasation of fluid (50). Histamine acts on H1-receptors of endothelial cells and sensory nerves, leading to the development of wheals. Further, it induces the symptoms of pruritus and neurogenic flare (10). Inflammation infiltrates the lesion site and longer lasting wheals are usually caused by the delayed secretion of inflammatory cytokines (10, 50). At the wheal site, dilatation of postcapillary venules and lymphatic vessels occurs in the upper dermis, and oedema in the upper- and mid-dermis (10). An inflammatory infiltration of neutrophils, eosinophils, macrophages and T cells can also be identified at the wheal site.

The pathogenesis of psoriasis has not been completely defined. Previous research has suggested that psoriasis involves a complex immunological and inflammatory reaction, and epidermal hyperproliferation, which is influenced by genetic factors or environmental factors (infection, smoking, drugs, skin trauma and stress) (12, 13). The human leukocyte antigen (HLA-Cw6 allele/*HLA-Cw0602–Cw0613*), also known as 'psoriasis susceptibility 1' (PSORS1), is the key susceptibility gene for psoriasis (51). The most likely pathogenesis of psoriasis involves the following process. T cells are activated and migrate into the skin after the activation of elements of the innate immune system (keratinocytes and dendritic cells) (12, 52). Certain functional T-cell subpopulations (type 1 helper T cell and type 17 helper T cell, that is, Th1 and Th17) grow under the influence of interleukin (IL)-12 and IL-23 (12, 52). Pro-inflammatory cytokines (tumour necrosis factor α, IL-17 and IL-22) secreted by Th1 cells and Th17 cells may promote the inflammatory process in psoriasis. The local cells (such as endothelial cells, fibroblasts and keratinocytes) involved in the inflammatory process will then enhance the cutaneous immune response through expression of adhesion molecules and other mediators (12, 52).

2.4 Diagnosis of Chronic Urticaria and Psoriasis Vulgaris

2.4.1 Chronic Urticaria

The diagnosis of chronic urticaria is based on a comprehensive patient history and clinical examination (8, 10). The history should include information about the clinical features of disease, medication usage and family history. The clinical manifestations of disease include the onset and duration of symptoms, frequency and characteristics of wheals (shape, size and distribution) and presence of itch or pain (10).

Clinical examination for diagnosis mainly consists of laboratory tests. Routine diagnostic tests for chronic spontaneous urticaria include differential blood count, erythrocyte sedimentation rate or C-reactive protein (8, 10). Additional tests could be taken into consideration when indicated by patient history or when a differential diagnosis is needed. These tests include autologous serum skin test, pseudo-allergen-free diet, functional auto-antibodies, thyroid hormones and auto-antibodies. For inducible urticarias, diagnostic tests are used to confirm the threshold for the triggers or eliciting factors, in addition to differential blood count, erythrocyte sedimentation rate or C-reactive protein (10).

2.4.2 Psoriasis Vulgaris

The diagnosis of plaque psoriasis (psoriasis vulgaris) is based on typical lesion morphology and clinical history (12, 53). Consultations that investigate the onset of lesions, possible triggering contributors, related symptoms (that is, itch, pain, sensitivity and irritation) and family history are necessary (53). The Auspitz sign is regarded as the key to diagnosing psoriasis. It comprises numerous symptoms: red plaques covered with silvery-white scales; a candle wax phenomenon that appears after scratching; punctate bleeding that occurs when the outer-most layer of skin is removed; pinpoint bleeding (12). Differential diagnosis should focus on nummular eczema, tinea, mycosis fungoides and pityriasis rosea. Predilection sites (scalp, trunk, buttocks and limbs) and the nails manifestation may aid diagnosis. To confirm diagnosis, a biopsy may be necessary (12). Psoriasis vulgaris may develop into or accompany other types of psoriasis. The phenotypes of psoriasis are based on historical morphologic descriptions (13).

2.5 Subtypes/Classification

2.5.1 Chronic Urticaria

According to the triggers of onset, chronic urticaria can be classified as spontaneous (chronic spontaneous urticaria) and inducible (10). The clinical manifestations of chronic spontaneous urticaria are not different to those of acute urticaria (37) and occur without eliciting factors. Many factors can trigger chronic inducible urticaria, with subtypes of inducible urticaria named according to their triggers. Subtypes include cold urticaria, heat urticaria, aquagenic urticaria, solar urticaria, symptomatic dermographism, delayed pressure urticaria, vibratory angioedema, cholinergic urticaria and contact urticaria. Temperature is a common factor to induce urticaria, where exposure to cold wind/water or heat may result in cold urticaria or heat urticaria. Similarly, solar urticaria is triggered by exposure to sunlight. Symptomatic dermographism is caused by pressure applied to the skin or minor trauma. Sitting or tight clothing may induce delayed pressure urticaria. Vibratory angioedema is associated with the use of vibrating tools. The occurrence of cholinergic urticaria is due to exercise or emotional change. The intake of food or interaction with animals can cause contact urticaria. Contact with water can also trigger aquagenic urticaria, regardless of water temperature (10).

2.5.2 Psoriasis Vulgaris

Psoriasis can be classified into different subtypes based on visual lesion morphology and symptoms. The features of each subtype are described below.

Plaque

Plaque psoriasis (psoriasis vulgaris) is the most common type, observed in approximately 80 to 90% of patients (13). Plaque psoriasis appears as sharply marginated, erythematous patches or plaques with characteristic silvery-white micaceous scales (53). The plaques are

irregular and round or oval. Most are often located on the scalp, trunk, buttocks and limbs, especially on extensor surfaces such as the elbows and knees (13). Active inflammatory psoriasis is characterised by the Koebner phenomenon, with new lesions occurring or developing at sites of trauma or pressure (54).

Inverse

Inverse psoriasis may commonly appear in the inframammary and abdominal folds, groin, axillae and genitalia. Lesions are erythematous plaques with little scales (12, 13).

Erythodermic

Chronic plaque psoriasis may develop into erythrodermic psoriasis. The patients' entire body surface area could nearly be covered with erythema, accompanied by varying degrees of scaling. The dysfunction of erythrodermic skin might lead to hypothermia and dehydration (13).

Pustular

Pustular psoriasis consists of generalised and localised lesions. The widespread pustules may be solitary on an erythematous background. If the pustules coalesce, accompanied by fever and toxicity, it is known as psoriasis pustulosa generalisata (von Zumbusch pustular psoriasis). In terms of localised pustular psoriasis, pustules develop on the palms of hands and/or soles of feet (12, 13).

Guttate

Guttate psoriasis typically manifests in dew-drop-like salmon-pink papules, usually 1–15 mm long, with a fine scale. It is found primarily on the trunk and the proximal extremities. Guttate psoriasis is triggered by β-haemolytic streptococcal infection. The disease is very

common during childhood or adolescence, which can transition into psoriasis vulgaris (12, 13).

Nail disease

The characteristics of nail psoriasis include pitting, onycholysis, subungual hyperkeratosis, and the oil-drop sign. Psoriatic disease of the fingernails is more common than toenails (50% v. 35% of all patients). It is observed in 90% of patients with psoriatic arthritis (13).

Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory seronegative spondyloarthropathy associated with psoriasis. The characteristics of PsA are stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons (dactylitis and enthesitis). The severity of the arthritis usually does not correlate with the skin disease. Nail damage is very common in PsA. The radiographic features of PsA mainly include joint erosions, joint space narrowing and bony proliferation (55).

2.6 Current Management for Chronic Urticaria and Psoriasis Vulgaris

2.6.1 Management for Chronic Urticaria

Management of chronic urticaria consists of two aspects: identification and avoidance of causes and triggers, and symptom control, which is recommended by five international guidelines (8, 10, 11, 56, 57). Once the eliciting factor has been identified for inducible urticarias, it is advised that the trigger be avoided (8, 10, 11). Practically, this may be virtually impossible, especially when the threshold of exposure that triggers urticaria is low (56). As the cause of chronic spontaneous urticaria is unlikely to be identified, treatment is aimed at controlling the symptoms (11, 56).

Management of chronic urticaria is with a 'step-care' approach (8, 10, 11). A step change occurs when symptom control is inadequate or when greater control is needed (see Table 2.1). Overall, there is a consensus that oral non-sedating second-generation H1 antihistamines are first-line therapy for chronic urticaria, with a low level of side effects (23).

While oral pharmacotherapy is the mainstay of treatment for chronic urticaria, other treatments are available and can be used in addition to antihistamine therapy. These include phototherapy (ultraviolet [UV]-A, psoralen and ultraviolet A [PUVA] and narrow-band ultraviolet [UV]-B] [10, 57]), topical antipruritic lotions to soothe itch (11, 56) and relaxation therapies (11, 56).

Table 2.1: A 'Step-care' Approach to Treatment

Step	**Treatment**
First-line therapy	Second-generation antihistamines
Transfer to second-line therapy if symptoms persist after two weeks	
Second-line therapy	Increased dosage (up to fourfold) of second-generation antihistamines
Transfer to third-line therapy if symptoms persist after 1–4 weeks	
Third-line therapy	Omalizumab
	Cyclosporin A
	Montelukast
	Short course systemic corticosteroid (max 10 days)

Adapted from the EAACI/GA^{2}LEN/EDF/WAO Guideline (10)

2.6.2 Management for Psoriasis Vulgaris

Psoriasis cannot be cured, so the main goal of treatment is to relieve symptoms, reduce relapse rates with minimal side effects, improve QoL and reduce comorbidity (12). Management of psoriasis depends on a variety of factors, such as disease severity, comorbidities, patient preference or opinion, realistic expectations about the efficacy of therapy and the use of other medication (12). Many treatment options exist for the management of psoriasis vulgaris. Topical applications are typically used for mild disease, phototherapy for moderate disease and systemic agents for severe disease (12).

Commonly used topical medications include vitamin D3 and vitamin D3-analogues, calcineurin inhibitors, corticosteroids, tazarotene, dithranol/anthralin, coal tar, salicylic acid and non-medicated topical moisturisers (12, 13). Phototherapy has also been used for the management of psoriasis vulgaris, which involves UV-A and UV-B wavelengths. Photochemotherapy, where psoralens from plants are administered before UVA phototherapy (PUVA), has been shown to be more effective for clearing psoriasis lesions than phototherapy alone (12, 58). Commonly used systemic medications include retinoids (vitamin A derivatives, such as acitretin), methotrexate (MTX), cyclosporine and fumaric acid esters. Systemic treatments, alone or in combination with topical treatments, are usually used for severe psoriasis vulgaris cases. Biologics such as TNF inhibitors and T-cell inhibitors are also used in the treatment of psoriasis vulgaris (12, 13, 55). Further, several therapies could be considered as complementary or alternative options, including climatotherapy and psychosocial therapy. However, the evidence of efficacy and safety is not sufficient (12).

2.6.3 Similarities in the Management of Chronic Urticaria and Psoriasis Vulgaris

Current management of chronic urticaria and psoriasis vulgaris is generally based on disease severity, QoL or patients' response. Biologics have been used in the treatment of both conditions.

2.7 Limitations of Current Management

2.7.1 Chronic Urticaria

Oral non-sedating second-generation H1 antihistamines are first-line therapy for chronic urticaria (23). However, debate on the treatment for refractory urticaria still exists (second-line therapy). Concerns involve the safety profile of updosing second-generation H1 antihistamines and the long-term use of first-generation H1 antihistamines (10, 23). In

addition, initiating adjunctive therapy with alternative agents remains a challenge for patients who do not respond to antihistamines. This mainly includes the risks of somnolence and psychomotor obstruction caused by first-generation H1 antihistamines as additional therapy to second-generation H1 antihistamines (10, 23). Evidence is lacking for third-line therapies and high costs have been noted for omalizumab and ciclosporin A (10, 23). Moreover, further studies are needed to evaluate the short-term use of systemic corticosteroids as third-line therapy for chronic urticaria or acute exacerbation (10).

2.7.2 Psoriasis Vulgaris

Although pharmacological therapy and phototherapy recommended by four international guidelines (12, 13, 55, 58) have been shown to be effective in short-term use, they often are associated with side effects when used long term. Two compound agents, such as calcipotriene/betamethasone dipropionate, have a better safety profile than single agents alone; however, studies have shown a high relapse rate (46.6%) (59). Oral retinoids (acitretin) have been associated with birth defects and liver damage. Further, oral MTX may cause liver toxicity and bone marrow suppression. NB-UVB phototherapy is associated with itching and blistering of the treated skin, irritation of the eyes and cold sores, while PUVA is associated with nausea, headache, fatigue, burning and itching. Biologics have been associated with a small increase in the risk of infection, tuberculosis and cardiac insufficiency. Clinical guidelines regard biologics as a third-line treatment for plaque psoriasis following inadequate response to topical treatment, phototherapy and non-biologic systemic treatments (12, 13).

2.7.3 Similarities in the Limitations of Current Management on Chronic Urticaria and Psoriasis Vulgaris

The conventional medical therapeutics for both conditions can provide rapid relief of symptoms. However, long-term use of conventional managements remains a challenge due to unpleasant side effects and lack of treatment response in some patients.

2.8 Summary

Chronic urticaria and psoriasis vulgaris are two common chronic skin conditions. They have similar prevalence (0.5–8.8% v. 0.47–8.5%) in global population. Both conditions inflict significant health-related (physical and psychological) and economic burdens on patients and healthcare systems.

First-line therapy for chronic urticaria is second-generation H1 antihistamines (23). Updosing of second-generation H1 antihistamines or initiating adjunctive therapy with alternative agents are considered for refractory urticaria (10, 23). Current treatment options for psoriasis vulgaris are mainly based on disease severity. Generally, topical agents are applied for mild disease, phototherapy for moderate disease and systemic agents or biologics for severe disease (12).

Conventional therapies could provide rapid temporary relief of symptoms for most patients with these conditions. However, as recurrence or exacerbation of both conditions is likely, long-term conventional management is required. This may lead to undesirable adverse events (AEs) or lack of treatment response from some patients. Therefore, patients may seek CAM treatment options. Studies indicate the use of CAM, including herbal medicine for skin conditions, is increasing (24–26).

Chapter 3. Chronic Urticaria and Psoriasis Vulgaris in Chinese Medicine

The contents for this chapter have been published in two books in the *Evidence-based clinical Chinese medicine* series: Volume 2 *Psoriasis vulgaris* (60) and Volume 3 *Chronic urticaria* (61).

3.1 Introduction of Chronic Urticaria and Psoriasis Vulgaris

The CM term for urticaria is '*yin zhen*' 瘾疹. There has been little change in terminology over time. *Yin zhen* 瘾疹 has been cited throughout classical CM literature and is the most likely of all classical terms to correspond with the modern understanding of urticaria (62, 63). Urticaria is usually associated with either internal or external wind. Wind as a pathogenic factor is characterised by a sudden onset of and rapid changes in symptoms. When resulting from an internal deficiency, it often leads to dryness. A constitutional weakness, inherited at conception and/or during pregnancy, may predispose a person to urticaria.

'Bai bi' 白疕 is the most likely of all classical terms to correspond with the modern understanding of psoriasis (63, 64). Despite diversity in the understanding of the pathogenesis of psoriasis, the fundamental pathogenesis is attributed to Blood syndromes. Blood originates from the food *qi* 气 produced by the Spleen. Through the descent of Lung *qi*, the food *qi* is sent to the Heart and transformed into Blood. Blood performs a nourishing and moistening function. Besides the nourishing action of *qi*, Blood can moisten the skin and hair, which ensures the tissues are not too dry (65). Multiple pathogenic factors may cause Blood heat, Blood deficiency or Blood stasis, which will affect the function of Blood.

3.2 Aetiology and Pathophysiology

3.2.1 Chronic Urticaria

Urticaria can be caused by constitutional weakness, deficiency of *qi* and Blood or failure of defensive *qi* in protecting the exterior (66–68). Urticaria may develop because of an external pathogenic attack, where the defensive *qi* is unable to prevent the pathogen from entering the body through the pores of the skin. When deficiency of defensive *qi* is prolonged, the patient will become more susceptible to repeated external wind attacks (chronic urticaria). Wind dries the skin, leading to the development of wheals and pruritus (66, 67).

An underlying deficiency or constitutional weakness can lead to the development of internal wind (66, 67). Urticarial wheals can occur when a deficiency of Blood fails to nourish the skin or when internal wind dries the skin. Overindulgence in spicy or fatty foods or seafood can impair the transforming and transporting functions of the Stomach and Spleen, leading to dampness. Subsequently, dampness can transform into heat when prolonged, which may further lead to internal wind. Dampness can also stagnate in the skin, with a clear fluid exuding from the wheals (66, 67).

Emotional disharmony can lead to *qi* stagnation, which can develop into heat over time and cause wind (66–68). When heat stagnates in the Heart channel, this can lead to fire, which enters the Blood. Heat in the Blood can dry the skin and may turn to wind. Finally, disharmony between the ‘Thoroughfare vessel’ (*Chong mai* 冲脉) and ‘Conception vessel’ (*Ren mai* 任脉) fails to adequately nourish the skin. This, combined with defensive *qi* deficiency, leads to the development of wheals when external wind attacks or internal wind is provoked (66, 67).

3.2.2 Psoriasis Vulgaris

Blood heat can be caused by multiple factors. For instance, depression and long-term emotional disturbance causes stasis of *qi*, which can transform into heat and result in Heart Fire. Overindulgence in seafood or meat may lead to disharmony between the Spleen and Stomach, resulting in stagnation of *qi*, which can transform into heat (69, 70). For people with a constitutional predisposition to Blood heat syndromes, the coupling of a Blood heat syndrome with an external invasion of wind can cause internal wind, leading to dryness. Wind-dryness will exhaust the body fluids and Blood, resulting in further *yin* 阴 deficiency and Blood dryness. Therefore, the lack of nourishment from body fluids and Blood will lead to the psoriasis symptoms of dry skin and scaly skin (71). Heat in the nutrient Blood can scorch the fluid and result in Blood stasis. Long-term Blood stasis may transform into heat and exacerbate Blood heat. Blood stasis is an important factor when the disease is complicated and/or of prolonged duration (64, 72, 73).

3.2.3 Similarities in Chronic Urticaria and Psoriasis Vulgaris

Both chronic urticaria and psoriasis vulgaris share the same pathogenesis of an underlying deficiency with an external pathogenic factor. The onset and progress are closely associated with deficiency of healthy, protective *qi* and external pathogen attack. The deficiency of healthy *qi* makes the body vulnerable to attack from factors such as wind, cold and dampness, resulting in urticaria syndrome of various types: exterior heat, exterior cold and dampness heat. In psoriasis, the deficiency of healthy *qi* allows invasion by toxic pathogens, with the syndrome types of Blood heat, Blood stasis and Blood dryness.

3.3 Syndrome Differentiation and Treatments

3.3.1 Chronic Urticaria

Syndrome differentiation is an important feature of diagnosis in CM dermatology. The *Standard of diagnosis and assessment of treatment effects of dermatological conditions in Chinese medicine* (中医皮肤科病证诊断疗效标准) was published in 1994 by the State Administration of Traditional Chinese Medicine of the People's Republic of China. This book identified the main syndrome types of *yin zhen* 瘾疹 (urticaria) as 'syndrome of wind-heat attacking the exterior' (exterior heat syndrome), 'syndrome of blockage of the exterior by wind and cold' (exterior cold syndrome) and 'syndrome of Blood deficiency and wind-dryness' (63). In 2012, the China Association of Chinese Medicine issued the *Guidelines for diagnosis and treatment of common diseases of dermatology in traditional Chinese medicine* (中医皮肤科常见病诊疗指南) (62). In addition to the two exterior syndromes described above, four additional syndrome types have been described in this guideline. These include 'damp-heat in Stomach and Intestine', 'defense-exterior insecurity' (defensive *qi* deficiency), 'deficiency of *qi* and Blood', and '*qi* and Blood stagnation and stasis' (62).

CM guidelines do not distinguish between acute and chronic urticaria. Rather, diagnosis is made according to traditional CM principles. The treatment principle for urticaria should identify whether the condition is one of 'exterior or interior', 'cold or heat', 'defense, *qi*, nutrient or Blood', 'the tip or root', 'acute or chronic', or 'healthy *qi* (*zheng qi* 正氣) deficiency or pathogen excess' (62). The treatment of chronic urticaria is largely reliant on identification of the underlying deficiency syndrome type. Therefore, treatment principles should include 'tonify *qi* and secure the exterior', 'tonify *yin* and moisten dryness', and 'dispel wind and stop itch' (67).

3.3.2 Psoriasis Vulgaris

For psoriasis vulgaris, the *Standard of diagnosis and assessment of treatment effects of dermatological conditions in Chinese medicine* (中医皮肤科病证诊断疗效标准) stated that the main syndrome types of *Bai bi* (psoriasis) were 'wind-heat and Blood dryness', 'Blood deficiency and wind-dryness' and 'stasis in the skin' (63). In 2011, *Evidence-based guidelines of clinical practice in Chinese medicine* (中医循证临床实践指南), published by the Chinese Academy of Chinese Medicine, also described the same syndromes (64). In describing the treatment principles for these syndromes, slightly different terminology was used (Blood heat, Blood dryness and Blood stasis). However, the clinical presentations were consistent with the described syndromes (64). Findings from a review of syndromes included reports of expert experience, case control studies and RCTs from 1979–2010. The review indicated that Blood heat, Blood dryness and Blood stasis were the basic syndrome types (74). Therefore, the treatment principle of psoriasis vulgaris mainly targets the Blood.

3.3.3 Similarities in Chronic Urticaria and Psoriasis Vulgaris

The external manifestation of chronic urticaria and psoriasis vulgaris results from a combination of both internal and external causes, with the deficiency of healthy *qi* as the underlying cause or root of the disease. The overall treatment principle of these two conditions should 'deal with superficial symptoms for acute conditions, and deal with the root for chronic condition; treatment should focus both on superficial symptoms and the root (急则治其标，缓则治其本，标本兼治，治病必求于本)' (65).

The following guidelines on the diagnosis and treatment of chronic urticaria and psoriasis vulgaris were used as references in the following section. They include the *Standard of diagnosis and assessment of treatment effects of dermatological conditions in Chinese*

medicine (中医皮肤科病证诊断疗效标准), published in 1994 by the State Administration of Traditional Chinese Medicine of the People's Republic of China (63), *Evidence-based guidelines of clinical practice in Chinese medicine* (中医循证临床实践指南), published by the Chinese Academy of Chinese Medicine (64), and the *Guidelines for diagnosis and treatment of common diseases of dermatology in traditional Chinese medicine* (中医皮肤科常见病诊疗指南), published by the China Association of Chinese Medicine (62).

Note that the use of some herbs, such as *ma huang* 麻黄, may be restricted in some countries. In addition, some herbs, such as *bai ji li* 白蒺藜, are restricted under the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora. Readers are advised to comply with relevant regulations.

3.4 Oral Chinese Herbal Medicine Treatment Based on Syndrome Differentiation

3.4.1 Chronic Urticaria

Exterior Heat Syndrome

Definition: Invasion of exterior part of the body by wind-heat (75).

Clinical manifestations: Fresh red skin rashes, pruritus accompanied by fever, sore throat, dry mouth and upset mood. Heat or wind induces or exacerbates the condition, while cool or cold environments relieve it. Red tongue with a thin white or yellow coating, superficial and rapid pulse (62, 66, 68, 76, 77).

Treatment principle: Dispel wind and clear heat, cool Blood and stop itch (62).

Formula: Modified *Xiao feng san* 消风散 (62, 68) and modified *yin qiao san* 银翘散 (62, 76, 77).

Herbs: Herb ingredients were not listed for each formula. Herbs included in both formulae include *sheng di huang* 生地黄, *fang feng* 防风, *chan tui* 蝉蜕, *zhi mu* 知母, *jing jie* 荆芥, *niu bang zi* 牛蒡子, *shi gao* 石膏, *jin yin hua* 金银花, *lian qiao* 连翘, *chi shao* 赤芍, *mu dan pi* 牡丹皮, and *huang qin* 黄芩.

Main actions of herbs: *Sheng di huang* 生地黄, *chi shao* 赤芍 and *mu dan pi* 牡丹皮 clear heat, cool the Blood and relieve toxicity. *Jin yin hua* 金银花, *lian qiao* 连翘 and *huang qin* 黄芩 clear heat and relieve toxicity. *Jing jie* 荆芥, *fang feng* 防风, *niu bang zi* 牛蒡子 and *chan tui* 蝉蜕 disperse external wind to stop itch. *Shi gao* 石膏 and *zhi mu* 知母 clear *qi* level heat.

Manufactured medicines: *Xiao feng zhi yang ke li* 消风止痒颗粒 (76) and *Yin qiao jie du wan* 银翘解毒丸 (66).

Exterior Cold Syndrome

Definition: Invasion of exterior part of the body by wind-cold (75).

Clinical manifestations: Wheals are slightly red or pale, which is exacerbated by exposure to wind-cold or chilled water, and relieved by warmth. Other symptoms may include an aversion to wind and cold, and absence of thirst. The condition will be more severe in winter and mild in summer. Slightly red tongue, thin and whitish coating, superficial and tight pulse (62, 66, 68, 76, 77).

Treatment principle: Dispel wind and cold, regulate and harmonise protective and nutritive levels (62, 76, 77).

Formula: Modified *Gui zhi ma huang ge ban tang* 桂枝麻黄各半汤 (62, 68, 76, 77) and modified *Jing fang bai du san* 荆防败毒散 (62).

Herbs: Herb ingredients were not listed for each formula. Herbs included in both formulae include *gui zhi* 桂枝, *bai shao* 白芍, *sheng jiang* 生姜, *zhi gan cao* 炙甘草, *ma huang* 麻黄, *da zao* 大枣, *xing ren* 杏仁, *jing jie* 荆芥, *fang feng* 防风, *qiang huo* 羌活, *chan tui* 蝉蜕, and *ji li* 蒺藜.

Main actions of herbs: *Gui zhi* 桂枝 and *bai shao* 白芍 regulate and harmonise protective and nutritive levels. *Ma huang* 麻黄, *jing jie* 荆芥 and *fang feng* 防风 dispel external wind and cold. *Qiang huo* 羌活 dispels wind and removes dampness. *Chan tui* 蝉蜕 and *ji li* 蒺藜 disperse wind to stop itch. *Da zao* 大枣, *sheng jiang* 生姜 and *zhi gan cao* 炙甘草 regulate the Stomach and Spleen.

Dampness Heat in Stomach and Intestine

Definition: A syndrome caused by a combination of dampness and heat, affecting both the Stomach and Intestine (75).

Clinical manifestations: Wheals are fresh, red and spread throughout the whole body, with severe pruritus. Accompanying symptoms are abdominal pain and distention, diarrhoea, nausea, fatigue and decreased appetite. Scanty and brown urine, decreased bowel movements. Red tongue with yellowish and greasy coating, slippery and rapid pulse, or soft and rapid pulse (62, 66, 68, 76, 77).

Treatment principle: Clear and relieve exterior and interior, promote bowel movement and drain dampness (62).

Formula: Modified *Fang feng tong sheng san* 防风通圣散 (62, 68) and modified *Chu shi wei ling tang* 除湿胃苓汤 (62).

Herbs: Herb ingredients were not listed for each formula. Herbs included in both formulae include *jing jie* 荆芥, *fang feng* 防风, *bai shao* 白芍, *da huang* 大黄 (to be added to decoction after the other herbs have been boiling for some time), *lian qiao* 连翘, *huang qin* 黄芩, *bai zhu* 白朮, *zhi zi* 栀子, *chen pi* 陈皮, *hou po* 厚朴, *di fu zi* 地肤子, *yi yi ren* 薏苡仁 and *gan cao* 甘草.

Main actions of herbs: *Jing jie* 荆芥 and *fang feng* 防风 disperse wind and release the exterior. *Da huang* 大黄 and *zhi zi* 栀子 clear heat and drain dampness, and promote bowel movement to relieve interior heat. *Lian qiao* 连翘 and *huang qin* 黄芩 clear heat and relieve toxicity. *Bai zhu* 白朮, *yi yi ren* 薏苡仁, *chen pi* 陈皮 and *hou po* 厚朴 tonify the Spleen *qi* and drain dampness. *Di fu zi* 地肤子 clears heat and removes dampness. *Gan cao* 甘草 harmonises each herb.

Manufactured medicines: *Fang feng tong sheng wan* 防风通圣丸 (62).

Defense-Exterior Insecurity

Definition: A syndrome characterised by symptoms such as spontaneous sweating, lack of strength and shortness of breath (75).

Clinical manifestations: Wheals are mostly small. Patients have spontaneous sweating and are prone to colds. Skin rash occurs after sweating or is induced by wind and cold. Pale tongue with thin, white coating, sunken and fine pulse (62, 76).

Treatment principle: Tonify *qi* and secure the exterior, dispel wind and cold (62).

Formula: Modified *Yu ping feng san* 玉屏风散 plus *Gui zhi tang* 桂枝汤 (62).

Herbs: Modified *Yu ping feng san* 玉屏风散: *huang qi* 黄芪, *bai zhu* 白朮 and *fang feng* 防风.

Modified *Gui zhi tang*: *gui zhi* 桂枝, *bai shao* 白芍, *sheng jiang* 生姜, *da zao* 大枣, *gan cao* 甘草, *zhi ma huang* 炙麻黄, *jing jie* 荆芥, *chan tui* 蝉蜕, *ji li* 蒺藜, *dang gui* 当归, *wu mei* 乌梅 and *wu wei zi* 五味子.

Main actions of herbs: *Huang qi* 黄芪 tonifies Lung and Spleen *qi* to secure exterior. *Wu mei* 乌梅 and *wu wei zi* 五味子 stop sweating. *Bai zhu* 白朮 tonifies Spleen *qi* to assist securing the exterior. *Fang feng* 防风 and *zhi ma huang* 炙麻黄 dispel external wind and cold. *Gui zhi* 桂枝 and *bai shao* 白芍 regulate and harmonise the protective and nutritive levels. *Da zao* 大枣, *sheng jiang* 生姜 and *gan cao* 甘草 regulate Stomach and Spleen. *Chan tui* 蝉蜕 and *ji li* 蒺藜 disperse wind to stop itch.

Manufactured medicines: *Yu ping feng ke li* 玉屏风颗粒 (62).

Dual Deficiency of Qi *and Blood*

Definition: A syndrome characterised by symptoms such as listlessness, shortness of breath, weakness and dizziness (75).

Clinical manifestations: Recurrent wheals lasting several months or years. The condition occurs in the afternoon or evening, or when the individual is tired. Patients usually have weak constitutions. Generalised symptoms include pale face, palpitations, insomnia, fatigue and disturbed appetite. Pale tongue with thin white coating, soft and fine pulse, or fine and weak pulse (62, 76, 77).

Treatment principle: Tonify *qi* and nourish Blood, tonify Heart and Spleen (62).

Formula: Modified *Ba zhen tang* 八珍汤 plus *Dang gui yin zi* 当归饮子 (62).

Herbs: Herb ingredients were not listed for each formula. Herbs included in both formulae include *dang gui* 当归, *chuan xiong* 川芎, *bai shao* 白芍, *shu di huang* 熟地黄, *huang qi* 黄芪, *dang shen* 党参, *bai zhu* 白朮, *fu ling* 茯苓, *he shou wu* 何首乌, *zhi gan cao* 炙甘草, *ji li* 蒺藜, *fang feng* 防风, and *chan tui* 蝉蜕.

Main actions of herbs: *Dang shen* 党参 and *shu di huang* 熟地黄 tonify *qi* and nourish Blood. *Bai zhu* 白朮 and *fu ling* 茯苓 tonify Spleen and drain dampness. *Dang gui* 当归, *he shou wu* 何首乌 and *bai shao* 白芍 nourish Blood and harmonise nutritive level. *Chuan xiong* 川芎 invigorates Blood and promotes *qi* movement. *Fang feng* 防风, *chan tui* 蝉蜕 and *ji li* 蒺藜 disperse wind to stop itch. *Zhi gan cao* 炙甘草 harmonises each herb.

Manufactured medicines: *Ba zhen he ji* 八珍合剂 (mixture) (76).

Qi-*Blood Stagnation and Stasis*

Definition: A syndrome characterised by symptoms such as dark or purple wheals.

Clinical manifestations: Dark or purple-red wheals typically occur around the waist and wrists due to pressure from belts and watches. Generalised symptoms include a dull face or

blue-violet lips, dry mouth and reduced desire to drink. Symptoms for women include irregular menstruation and dysmenorrhea, with purple-red or blood clots. Dark purple tongue with petechia or ecchymosis, little coating, fine and rough pulse (62, 76).

Treatment principle: Regulate *qi* and invigorate Blood, dispel wind and stop itch (62).

Formula: Modified *Xue fu zhu yu tang* 血府逐瘀汤 (62).

Herbs: *Dang gui* 当归, *sheng di huang* 生地黄, *tao ren* 桃仁, *hong hua* 红花, *zhi ke* 枳壳, *chi shao* 赤芍, *chai hu* 柴胡, *chuan xiong* 川芎, *di long* 地龙, *bai xian pi* 白鲜皮, *di fu zi* 地肤子, *wu shao she* 乌梢蛇, *chan tui* 蝉蜕 and *gan cao* 甘草.

Main actions of herbs: *Dang gui* 当归, *chi shao* 赤芍, *chuan xiong* 川芎, *tao ren* 桃仁 and *hong hua* 红花 invigorate the Blood and transform Blood stasis. *Chai hu* 柴胡 and *zhi ke* 枳壳 soothe the Liver and regulate *qi*. *Sheng di huang* 生地黄 and *dang gui* 当归 nourish the *yin* and moisten dryness, preventing loss of *yin* by removing Blood stasis. *Di long* 地龙, *chan tui* 蝉蜕 and *wu shao she* 乌梢蛇 disperse wind to stop itch. *Bai xian pi* 白鲜皮 and *di fu zi* 地肤子 clear heat, remove dampness and stop itch. *Gan cao* 甘草 harmonises each herb.

Blood Deficiency and Wind-Dryness

Definition: A syndrome characterised by symptoms such as dry and itchy skin, lustreless complexion and pale nails (75).

Clinical manifestations: The condition occurs repeatedly, with a long duration. The skin rash is exacerbated in the afternoon or evening. Can be accompanied by emotional upset and irritability, dry mouth, feverishness in palms and soles; red tongue with scanty fluid, deep and fine pulse (66, 68).

Treatment principle: Nourish Blood and dispel wind, moisten dryness and stop itch (68).

Formula: Modified *Dang gui yin zi* 当归饮子 (68).

Herbs: *Dang gui* 当归, *sheng di huang* 生地黄, *bai shao* 白芍, *chuan xiong* 川芎, *he shou wu* 何首乌, *jing jie* 荆芥, *fang feng* 防风, *bai ji li* 白蒺藜, *huang qi* 黄芪 and *sheng gan cao* 生甘草.

Main actions of herbs: *Dang gui* 当归, *he shou wu* 何首乌 and *huang qi* 黄芪 nourish the Blood and moisten dryness. *Sheng di huang* 生地黄, *bai shao* 白芍 and *chuan xiong* 川芎 clear heat, cool and invigorate the Blood. *Jing jie* 荆芥, *fang feng* 防风 and *bai ji li* 白蒺藜 dispel wind. *Sheng gan cao* 生甘草 clears heat and harmonises the actions of the other herbs.

3.4.2 Psoriasis Vulgaris

Blood Heat

Clinical manifestations: New bright red papules or maculopapules of varying sizes develop continuously, Auspitz's sign appears when the scale is removed and there is an occasional occurrence of Koebner's phenomenon. Accompanying symptoms include itching, anxiety, dry mouth, constipation, yellow urine and red tongue with yellow or greasy coating. The pulse is slippery, stringy or rapid (63, 64, 78, 79).

Treatment principle: Clear heat and cool the Blood, relieve toxicity and reduce erythema (78, 79).

Formula: Modified *Xiao feng san* 消风散 plus *Xi jiao di huang tang* 犀角地黄汤 (78, 79) and modified *Liang xue di huang tang* 凉血地黄汤 (62).

Herbs: *Dang gui* 当归, *sheng di huang* 生地黄, *fang feng* 防风, *chan tui* 蝉蜕, *zhi mu* 知母, *ku shen* 苦参, *hu ma ren* 胡麻仁, *jing jie* 荆芥, *cang zhu* 苍术, *niu bang zi* 牛蒡子, *shi gao* 石膏, *xi jiao* 犀角 [*shui niu jiao* instead 水牛角代], *chi shao* 赤芍 and *mu dan pi* 牡丹皮

Main actions of herbs: *Sheng di huang* 生地黄, *shui niu jiao* 水牛角, *chi shao* 赤芍 and *mu dan pi* 牡丹皮 clear heat, cool the Blood and relieve toxicity. *Dang gui* 当归 and *hu ma ren* 胡麻仁 nourish the Blood and moisten dryness. *Jing jie* 荆芥, *fang feng* 防风, *niu bang zi* 牛蒡子 and *chan tui* 蝉蜕 disperse external wind to stop itch. *Cang zhu* 苍术 and *ku shen* 苦参 clear damp-heat. *Shi gao* 石膏 and *zhi mu* 知母 clears *qi* level heat.

Manufactured products: *Fu fang qing dai wan* 复方青黛丸 (pill) (64, 67) and *Qing kai ling zhu she ye* 清开灵注射液 (IV injection) (64, 67).

Blood Dryness

Clinical manifestations: Long-term disease, lesions manifest as light red and patchy, covered with plenty of dry silvery-white scales. Parts of lesions have disappeared. Dry and chapped skin with itch or pain. Accompanying symptoms include dry mouth, constipation; red tongue body with thin and white coating. The pulse is wiry and slow (63, 64, 78, 79).

Treatment principle: Tonify *yin* and nourish the Blood, moisten dryness and dispel wind (78, 79).

Formula: Modified *Dang gui yin zi* 当归饮子 (62, 78) and *Yang xue run fu yin* 养血润肤饮 (62).

Herbs: *Dang gui* 当归, *sheng di huang* 生地黄, *bai shao* 白芍, *chuan xiong* 川芎, *he shou wu* 何首乌, *jing jie* 荆芥, *fang feng* 防风, *bai ji li* 白蒺藜, *huang qi* 黄芪, *sheng gan cao* 生甘草, *tian dong* 天冬, *mai dong* 麦冬, *tian hua fen* 天花粉.

Main actions of herbs: *Dang gui* 当归, *he shou wu* 何首乌 and *huang qi* 黄芪 nourish the Blood and moisten dryness. *Sheng di huang* 生地黄, *bai shao* 白芍 and *chuan xiong* 川芎 clear heat, cool and invigorate the Blood. *Jing jie* 荆芥, *fang feng* 防风 and *bai ji li* 白蒺藜 dispel wind. *Tian dong* 天冬, *mai dong* 麦冬 and *tian hua fen* 天花粉 tonify *yin* and moisten dryness. *Sheng gan cao* 生甘草 clears heat and harmonises the actions of the other herbs.

Manufactured products: *Xiao yin ke li* 消银颗粒 (granule) (64), *Dang gui zhu she ye* 当归注射液 (IV injection) and *Shen mai zhu she ye* 参麦注射液 (IV injection) (67).

Blood Stasis

Clinical manifestations: The disease duration is long and at the stable stage, dull red, itchy, hard and thick plaques are covered by thick, dry, silvery-white scales. There are no obvious general symptoms but there is a dark purple or red tongue body with petechial spots. The pulse is uneven, or wiry and slow (63, 64, 78, 79).

Treatment principle: Invigorate the Blood and transform Blood stasis, nourish the Blood and moisten dryness (67, 78, 79).

Formula: Modified *Tao hong si wu tang* 桃红四物汤 (67, 78, 79).

Herbs: *Shu di huang* 熟地黄, *dang gui* 当归, *bai shao* 白芍, *chuan xiong* 川芎, *tao ren* 桃 and *hong hua* 红花.

Main actions of herbs: *Shu di huang* 熟地黄 tonifies the *yin* and nourishes the Blood. *Bai shao* 白芍 tonifies the Liver, Blood and preserves the *yin*. *Dang gui* 当归 tonifies the Blood and nourishes the Liver. *Chuan xiong* 川芎 invigorates the Blood and promotes the movement of *qi*. *Tao ren* 桃仁 and *hong hua* 红花 have a very strong effect on invigorating the Blood and transforming Blood stasis.

Manufactured products: *Lei gong teng duo gan pian* 雷公藤多苷片 (tablets) (67) and *Dan shen zhu she ye* 丹参注射液 (IV injection) (64, 67).

3.5 Topical Chinese Herbal Medicine Treatment

3.5.1 Chronic Urticaria

Calamine lotion could be used topically (68).

3.5.2 Psoriasis Vulgaris

In external CHM, psoriasis can be treated with topical preparations such as baths, fumigation and other methods. Among these, CHM ointments and CHM baths are the most commonly used therapies (64).

CHM ointment: Mild ointment or moisturiser could be used at the progressive stage (67, 78, 79), such as *Huang bo* ointment 黄柏膏, *Qing dai* ointment 青黛膏, *Qing dai ma you* 青黛麻油 (67, 79), *Shi du* ointment 湿毒膏, *Pu lian* ointment 普连软膏 or *Bing huang fu le* ointment 冰黄肤乐软膏 (64). For the stable and regressive stage, 10 % sulphur ointment could be used (67, 79).

CHM baths: Herbs used for CHM baths are usually based on syndrome differentiation. Herbs commonly used in CHM bath decoctions are *xu chang qing* 徐长卿, *qian li guang* 千

里光, *di fu zi* 地肤子, *huang bo* 黄柏, *she chuang zi* 蛇床子, *cang er zi* 苍耳子, *lang du* 狼毒, *bai xian pi* 白鲜皮, *tu jin pi* 土槿皮, and/or *huai hua* 槐花 (79).

3.6 Acupuncture and Other Chinese Medicine Therapies

In addition to CHM, acupuncture and other CM therapies are also used in the management of chronic urticaria and psoriasis vulgaris. An overview of acupuncture and other CM therapies recommended by clinical practice guidelines and textbooks is provided below.

3.6.1 Chronic Urticaria

Acupuncture and ear acupuncture have been recommended to treat urticaria. Other therapies that may be beneficial for urticaria include cupping therapy (see Table 3.1). There are several actions of key acupuncture points (65):

- LI11 *Quchi* 曲池—expels exterior wind, clear heat, cools Blood, resolves dampness, regulates nutritive *qi* and Blood.
- SP10 *Xuehai* 血海—cools Blood, removes Blood stasis and tonifies Blood.
- ST36 *Zusanli* 足三里—benefits the Stomach and Spleen, tonifies *qi* and Blood, dispels cold, regulates nutritive and defensive *qi*, expels wind and damp.

3.6.2 Psoriasis Vulgaris

Acupuncture and related therapies, including acupuncture (body and auricular) and acupuncture point injection therapy (the injection of a substance into an acupuncture point) have been recommended to treat psoriasis. Care must be taken when new lesions are developing because skin penetration may be more likely to result in Koebner's phenomenon.

Other therapies that may be beneficial for psoriasis include catgut embedding (embedding of fibre threads subcutaneously), pricking-to-bleed and cupping therapy (see Table 3.2). Some therapies are not commonly used outside China. Readers should comply with the relevant regulations before use.

Table 3.1: Summary of Acupuncture Therapies and other Chinese Medicine Therapies for Urticaria

Intervention	Acupuncture points/body area	Treatment frequency
Body acupuncture (67, 68)	LI11 *Quchi* 曲池, PC6 *Neiguan* 内关 can be used for urticaria in the upper part of the body; SP10 *Xuehai* 血海, ST36 *Zusanli* 足三里, SP6 *Sanyinjiao* 三阴交 can be used for urticaria in the lower part of the body; GB31 *Fengshi* 风市, GB20 *Fengchi* 风池, GV14 *Dazhui* 大椎, BL25 *Dachangshu* 大肠俞 can be used for the whole body	Not specified
Ear acupuncture (67, 68)	CO12 *Ganqu* 肝区, CO13 *Piqu* 脾区, CW7 *Shenshangxian* 肾上腺, AT4 *Pizhixia* 皮质下, TF4 *Shenmen* 神门, CO14 *Fei* 肺, CO18 *Neifenmi* 内分泌, *Kangguomindian* 抗过敏点 (anti-allergic point)	Not specified
Cupping (68)	CV8 *Shenque* 神阙	Once a day, 15 minutes for each treatment

Table 3.2: Summary of Acupuncture and other Chinese Medicine Therapies for Psoriasis

Intervention	Acupuncture points/body area	Treatment frequency
Body acupuncture (67, 78)	Main points: LI11 *Quchi* 曲池, LI4 *Hegu* 合谷, GV14 *Dazhui* 大椎, BL13 *Feishu* 肺俞, SP10 *Xuehai* 血海, SP6 *Sanyinjiao* 三阴交; supplementary points for lesions on the head and face: LI20 *Yingxiang* 迎香, GB20 *Fengchi* 风池, SI18 *Quanliao* 颧髎; supplementary point for lesions on upper limbs: TE6 *Zhigou* 支沟; supplementary points for lesions on lower limbs: ST36 *Zusanli* 足三里, ST40 *Fenglong* 丰隆	Treatment is applied once a day with 10 days as one treatment course
Auricular acupuncture (67,	CO14 *Fei* 肺, TF4 *Shenmen* 神门, CO18	Every other day, with 10 days as one treatment

78)	*Neifenmi* 内分泌, CO15 *Xin* 心, CO7 *Dachang* 大肠 etc.	course
Acupuncture point injection therapy (67)	*Dang gui zhu she ye* 当归注射液 (injection) can be injected into the points: BL13 *Feishu* 肺俞, LI11 *Quchi* 曲池, ST36 *Zusanli* 足三里	7–10 days as one treatment session, one week break between sessions
Catgut embedding (67)	Apply to acupuncture points, mainly on back and limbs	Not specified

3.7 Summary

In CM, the key principle of pathogenesis theory is that 'maintaining good health will help to prevent disease（正气存内，邪不可干）'. This principle is particularly relevant for dermatological conditions such as chronic urticaria and psoriasis vulgaris. The causes of disease can be internal (for example, organ dysfunction) or external (for example, exposure to environmental factors as cold, wind or emotional factors), or a combination of both. These two conditions share the same pathogenesis of an underlying deficiency with an external pathogenic factor. From a CM perspective, they also share the same treatment principle. Overlap in formulae recommended in clinical practice guidelines and textbooks was observed, with both *Xiao feng san* 消风散 and *Dang gui yin zi* 当归饮子 being recommended for both chronic urticaria and psoriasis vulgaris. These two conditions will provide valuable insight into CHM management of dermatological diseases.

Chapter 4. Data Mining of Classical Literature

Contents in this chapter have been included in two published books: *Evidence-based clinical Chinese medicine* series: Volume 2 *Psoriasis vulgaris* (60) and Volume 3 *Chronic urticaria* (61).

4.1 Chronic Urticaria and Psoriasis Vulgaris in Classical Literature

CM has a long history in the treatment of dermatological conditions such as chronic urticaria and psoriasis vulgaris. A wealth of information on clinical cases and relevant treatments in ancient times has been recorded in CM classical literature. Treatments for these conditions have included CHM and acupuncture. The descriptions of conditions and treatments in the classical literature continue to guide current clinical practice and drug discovery. For example, the herb *qing hao* 青蒿 was described as a malaria treatment in CM classical book *Zhou hou bei ji fang* 肘后备急方 (*Handbook of prescriptions for emergencies*) (363 AD). Inspired by this book, scientist Tu Youyou extracted artemisinin (also known as *qing hao su*) from *qing hao* 青蒿, which has been used globally to treat malaria. She was awarded the Nobel Prize for her breakthrough discovery.

To explore ancient CHM treatments for chronic urticaria and psoriasis vulgaris, a thorough exploration of CM classical works was required. The number of CM classical literature sources is vast. Digitalised collections provide greater access to the classical works, making systematic searches and evaluations more efficient to perform (80, 81). The *ZHYD* (*Encyclopaedia of traditional Chinese medicine*) was used in this study (82). This is the largest collection of CM classical literature, comprising more than 1,100 ancient and pre-modern CM electronic books on CD (80, 81). The *ZHYD* was used to identify formulae and

herbs recorded in classical citations that were most likely related to chronic urticaria and psoriasis vulgaris. This study aimed to provide evidence on CHM treatments for chronic urticaria and psoriasis vulgaris in ancient times through the data mining of classical literature. The findings from this study highlight treatments that could be considered for use in contemporary clinical practice.

4.2 Method

4.2.1 Identification of Search Terms

The terminology for chronic urticaria and psoriasis vulgaris in CM classical literature is not the same as language and labels used in modern times. To retrieve as many *ZHYD* citations as possible related to the targeted conditions, search terms included a set of all names potentially used to describe the conditions in ancient times. A list of terms referring to chronic urticaria and psoriasis vulgaris were identified after reviewing authoritative dictionaries, such as *Zhong xi yi bing ming dui zhao da ci dian* 中西医病名对照大辞典 (2002) (83) and *Zhong yi fang ji da ci dian* 中医方剂大辞典 (84). Contemporary CM works that focused on urticaria, psoriasis or dermatological conditions, including guidelines, key textbooks, monographs and journal articles, were hand searched. In addition, CM dermatologists were consulted to identify any additional search terms. A pilot search of each term was conducted to detect the accuracy in retrieving citations for urticaria and psoriasis. In the pilot search, no information on disease duration was found for the citations related to urticaria. Considering the complexity involved in identifying the specific citations of chronic urticaria (as opposed to acute urticaria), the search scope included both acute and chronic urticaria. After the pilot search, eight terms for urticaria and 13 terms for psoriasis vulgaris were selected for the formal search (see Tables 4.1 and 4.2).

Table 4.1: Terms Used to Identify Urticaria in Classical Literature Citations

Pinyin	Chinese characters
Pei lei 1	瘖瘾
Pei lei 2	瘖癗
Yin zhen 1	瘾疹
Yin zhen 2	隐疹
Feng cheng ge da	风乘疙瘩
Feng zhen kuai	风疹块
Bai zhen	白轸
Chi zhen	赤轸

Table 4.2: Terms Used to Identify Psoriasis Vulgaris in Classical Literature Citations

Pinyin	Chinese characters
Bai bi	白疕
Bai ke chuang	白壳疮
Bai xuan	白癣
Bi feng	疕风
Feng xuan	风癣
Gan xuan	干癣
Gou xuan	狗癣
Gou pi xuan	狗皮癣
Niu pi xuan	牛皮癣
She feng	蛇风
She shi	蛇虱
Song pi xuan	松皮癣
Yin qian feng	银钱疯

4.2.2 Search of the Zhong Hua Yi Dian

The psoriasis search was conducted in 2012, when the latest version of the *ZHYD* was the fourth edition. When the search for urticaria was conducted in 2014, the fifth edition had been released with software improvements, and this enhanced version was used for the urticaria search. Accordingly, the methods used differed, as described below.

Searching of the ZHYD involves search of terms one at a time. Search strategies which combine multiple terms, as used in electronic biomedical databases, are not possible. A comprehensive search of the *ZHYD* was conducted by entering the search terms (individually) into the search boxes for ‘headings’ (目录搜索) and ‘body text’ (正文搜索). Headings or text

containing search terms were retrieved, with the number of search terms hits (that is, each instance of the term) being displayed. The number of hits for each search term was recorded in a Microsoft Excel file. For psoriasis, search results were copied into a Word document manually and entered into the Excel spread sheet for further analysis. For urticaria, the search results were imported directly from the CD to a pre-defined Excel spreadsheet. The imported data included search terms (key words), the source (book title and chapter) and full text of the citation.

4.2.3 Data Management

For both conditions, the following information was extracted from the original citation in Excel: symptom description, formula name, formula ingredients and preparation type. Citations were screened to identify duplicates according to three criteria:

- If one citation was retrieved through both 'headings' and 'body text' search, it was deemed a duplicate.
- Several books have multiple names. If a citation appeared in a book that has multiple names in the *ZHYD*, it was marked as a duplicate. For instance, the *You ke zheng zhi zhun sheng* 幼科证治准绳 and the *Zheng zhi zhun sheng·you ke* 证治准绳·幼科 are the same book. However, both book names can be found in the *ZHYD*. In this instance, the citation would be considered a duplicate.
- If one citation was identified by multiple search terms, it was treated as one citation, and the multiple search terms that identified it were noted.

After removal of duplicates, citations that contained more than one herbal formula were separated into different rows in Excel for analysis. Citations written after 1949, and those that did not contain CHM treatment information, were excluded from further analysis.

4.2.4 Coding

To facilitate statistical analysis, text information of all citations was transferred into numerical data (codes and score). All citations related to urticaria and psoriasis vulgaris were coded using the same procedure (81). Codes were allocated to items according to a pre-defined coding system (81): book name, dynasty, treatment type (formula or multiple herbs; formula with no ingredients; single herb; other treatment), formula ingredients and search terms. Other descriptions of each citation were coded with 0 (unclear), 1 (yes) and 2 (not present). The coding items involved the administration of CHM and characteristics of each condition described in modern medical texts or clinical guidelines (see Table 4.3).

Table 4.3: Basic Information Coding for Classical Literature Citations

Chronic urticaria	**Psoriasis vulgaris**
Citation describes a topical CHM treatment?	Citation describes a topical CHM treatment?
Citation describes an oral CHM treatment?	Citation describes an oral CHM treatment?
Symptom 1: skin rash	Symptom 1: skin rash
Symptom 2: wheals	Symptom 2: red skin
Symptom 3: pruritus	Symptom 3: white skin
Symptom 4: history of similar occurrences	Symptom 4: scaly skin
Symptom 5: red skin	Symptom 5: itch
Symptom 6: sudden onset	Symptom 6: pain
Symptom 7: pain	Symptom 7: dry skin
Symptom 8: oedema/swelling	

Based on the symptoms described, each citation was evaluated to determine the likelihood of the citation being urticaria or psoriasis vulgaris. The judgment criteria of each condition were the presence of core symptoms mentioned in modern clinical guidelines (10, 13). For urticaria, possible urticaria citations referred to those describing both pruritus plus skin rash/wheals and any of the following symptoms: history of similar occurrences, red skin, sudden onset, and pain or oedema/swelling. If both wheals and pruritus were described in one citation, urticaria was considered most likely.

For psoriasis, each citation was allocated a code to represent the judgment (see Table 4.4). Citation was coded as '0' (no information to judge), '1' (most likely psoriasis vulgaris citation), '2' (not psoriasis citation), '3' (possible psoriasis vulgaris citation). Since most citations contained limited information or did not provide explicit descriptions of symptoms, it was not appropriate to make judgments on description of symptoms only. In addition, the symptoms of psoriasis may vary due to the type, stage and severity of the disease. Therefore, an overall judgment by two experienced clinicians was incorporated into the judgment criteria. Two clinicians took all citation data into consideration when making overall judgments. Any disagreements were resolved through discussion with a CM dermatology professor.

Table 4.4: Judgment Coding for Psoriasis Vulgaris Citations

Citation judgement	**Definition**
No information to judge	-
Not psoriasis	-
Possibly it is psoriasis	Both skin lesion/rash and scaly skin were described; clinician's overall judgment to be possible citations
Most likely it is psoriasis	Description of skin lesion/rash and scaly skin (as per possibly psoriasis citations; clinician's overall judgment to be most likely citations

Finally, all text data extracted from the *ZHYD* were converted into numerical codes, except for formula names in the citations related to urticaria. All data were transferred into Statistical Package for the Social Sciences software (SPSS) statistical analysis.

4.2.5 Statistical Analysis

Descriptive statistics were used to analyse data for CHM formulae and standardised herbal ingredients. Treatment information (formula and herb frequency) were analysed according to the judgment of possible or most likely urticaria/psoriasis. Formulae with identical names were regarded as the same formula when calculating the frequency of formulae, which

allowed variation in herb ingredients. The ingredient list was examined for each of the named formulae. Several formulae had variations in the herbal ingredients, although they shared the same formula name. In this instance, the herb ingredients of formulae cited by the earliest citation were listed. Where multiple variants of formulae ingredients were found in one book, all variants were presented. Further, where the herb ingredients were not available, these were sourced from another citation in the same book.

The standardisation of herbal ingredients was conducted using a nomenclature list of commonly used CHMs provided by the Chinese Medicine Board of Australia (CMBA). This list was last updated in September 2015. This was done to account for differences in herb names between classical literature and modern use. In addition, one herb could be described with multiple names in classical works. For instance, *wu shi* 恶实, *niu bang zi* 牛蒡子, *shu nian zi* 鼠粘子, *da li zi* 大力子 and *da niu zi* 大牛子 were various names of *Arctium lappa* L. used in ancient CM works. *Niu bang zi* 牛蒡子 is used currently and suggested by the CMBA. Therefore, other names of *Arctium lappa* L. were standardised to *niu bang zi* 牛蒡子. Excipients were also included in the analysis of herb frequency, such as *feng mi* 蜂蜜 (honey) and *zhu you* 猪油 (lard). While they did not possess specific therapeutic properties, they were important ingredients of the treatment and used to blend the herbs.

4.3 Results of Chronic Urticaria

4.3.1 Characteristics of Citations

Analysis of the *ZHYD* retrieved 2,285 instances of eight search terms (see Table 4.5). The greatest number of hits was produced by the search term *yin zhen* 1 瘾疹 (1,790 hits, 78.3%). Search terms '*feng cheng ge da* 风乘疙瘩', '*feng zhen kuai* 风疹块', '*bai zhen* 白轸' and '*chi*

zhen 赤轸' accounted for less than one per cent of all hits, which indicated these terms were not commonly used in classical terminology.

Table 4.5: Hit Frequency by Search Term for Urticaria

Pinyin	Chinese characters	Citation frequency n (%)
Yin zhen 1	瘾疹	1790 (78.3)
Yin zhen 2	隐疹	243 (10.6)
Pei lei 2	瘖癗	184 (8.0)
Pei lei 1	瘖癗	51 (2.2)
Feng zhen kuai	风疹块	11 (0.5)
Chi zhen	赤轸	3 (0.1)
Feng cheng ge da	风乘疙瘩	2 (0.1)
Bai zhen	白轸	1 (0.04)

After excluding duplicate citations and those irrelevant to urticaria, 881 citations considered possible urticaria citations (according to the pre-defined criteria) were retained. Of these citations, 332 included treatments (CHM and acupuncture) for urticaria. After citations containing multiple treatments were split into separate citations, 540 treatment citations were identified. Of these citations, 533 descriptions of CHM treatment were identified and seven citations were related to acupuncture therapies. Among these citations, 29 were deemed most likely to relate to urticaria because both wheals and pruritus were described in the citations.

Four search terms identified the 29 most likely urticaria citations: '*feng cheng ge da* 风乘疙瘩' (two citations), '*pei lei* 2 瘖癗' (seven citations), '*yin zhen* 1 瘾疹' (15 citations) and '*yin zhen* 2 隐疹' (five citations). Both citations identified by '*feng cheng ge da* 风乘疙瘩' were considered most likely urticaria citations. The earliest citation possibly related to urticaria treatment appeared in *Zhou hou bei ji fang* 肘后备急方 (*Handbook of prescriptions for emergencies*) (363 AD). The most recent citation was sourced from *Ben cao jian yao fang* 本草简要方 (1938).

4.3.2 Representative Citations

Yin zhen 1 (瘾疹) was described in *You you ji cheng* 幼幼集成 (1750) by Chen Fuzheng in the Qing dynasty. Chen pointed out the characteristics of the condition and its treatment as:

> *Yin zhen* comes out mostly due to [the] Spleen, which is faintly visible among the skin, with pruritus. It might not be red and commonly called as *feng dan* 风丹. *Jia wei qiang huo san* 加味羌活散 can be used. 清•陈复正《幼幼集成》 (1750) 瘾疹多属于脾, 以其隐隐在皮肤之间, 发而多痒。或不红者,俗人名为风丹。加味羌活散。.

The aetiology of *yin zhen* 1 瘾疹 was believed to be related to the Spleen, which aligns with current understandings. Contemporary literature indicates that dampness can trigger urticaria due to impairment of the transforming and transporting function of the Stomach and Spleen. *Jia wei qiang huo san* 加味羌活散 was suggested for the treatment; this formula is not used in contemporary literature.

In *Tong yuan yi shu wai ke* 彤园医书•外科 (1795), the symptoms, aetiology and treatments of *pei lei* 2 瘖癗 were described as:

> Pimple comes after pruritus. It looks like segments of a bean, which pile up to a larger area. The lesion is blush and swelling. Person with [a] deficiency of defensive exterior is more likely to suffer this condition due to [a] wind attack after sweating or laying without keeping warm. *Qin jiao niu bang tang* 秦艽牛蒡汤 is commonly used for the case with more pruritus at daily time, and *Dang gui yin* 当归饮 for the night case. 《彤园医书（外科）》(1795) 瘖癗,初起皮肤作痒,次发扁疙瘩,形如豆瓣,堆垒成片,红晕宣肿,由汗出受风或露卧乘凉,风邪多袭,表虚之人,每易患此。如日间痒甚,常服秦艽牛蒡汤 (见五卷云字号), 夜间痒甚,常服当归饮 (见五卷阳字号).

This citation provided a vivid description for pimples (wheals) that closely matches the appearance of urticaria described in conventional medicine textbooks.

4.3.3 Frequently Used Formulae and Herbs

Frequently Used Formulae in Possible Urticaria Citations

The administration of CHM in the 533 possible urticaria citations mainly included formulae for oral (274 citations, 51.4%) or topical use (220 citations, 41.3%). No description of administration method was provided for the remaining 39 citations. Among all citations, 326 herb formulae were identified, of which 55 were unnamed formulae. These were excluded from further analysis.

The most frequently cited formulae and their ingredients are presented in Tables 4.6 and 4.7. *Xiao feng san* 消风散 was the most frequently cited formula for oral use, described in 37 citations with six variants (see Table 4.6). The earliest citation of *Xiao feng san* 消风散 was found in *Tai ping hui min he ji ju fang* 太平惠民和剂局方 (1,107 AD). For topical application, *Mang cao gao* 莽草膏 was the most commonly reported formula (see Table 4.7). The earliest citation of *Mang cao gao* 莽草膏 was found in *Tai ping sheng hui fang* 太平圣惠方 (992 AD).

Table 4.6: Oral Formulae Frequently Used in Possible Urticaria Citations

Formula name	Route of administration	Herb ingredients	Citation frequency n
Xiao feng san	Oral	*Jing jie, fang feng, qiang huo, hou po, ren shen, jiang can, chuan xiong, gan cao, fu ling, huo xiang, chen pi, chan tui, jiang*	37
Hu ma san	Oral	*Hu ma, jing jie, bo he, ku shen, gan cao, wei ling xian, he shou wu, jiu, mi* (honey)	13
Hua pi san	Oral	*Hua pi, jing jie, zhi ke, gan cao, xing ren , jiu*	12
Zui xian san	Oral	*Hu ma, niu bang zi, man jing zi, gou qi zi, ji li, ku shen, gua lou, fang feng, cha*	9
Jia wei qiang huo san	Oral	*Qiang huo, qian hu, bo he, tian ma, chuan xiong, zhi ke, jie geng, chan tui, ren shen, gan cao, sheng jiang, fu ling*	8
Ren shen xiao feng san	Oral	*Ren shen, jing jie, gan cao, chen pi, jiang can, fu ling, fang feng, chuan xiong, huo xiang, chan tui, hou po, qiang huo*	5

Table 4.7: Topical Formulae Frequently Used in Possible Urticaria Citations

Formula name	Route of administration	Herb ingredients	Citation frequency n
Mang cao gao	Topical	Variant A: (3 citations): *Mang cao, chuan xiong, ku shen, dang gui, shuo diao, xi xin, fu zi, da ji, yuan hua, hua jiao, zhi zhu hua, zhu zhi, jing tian*	8
		Variant B (1 citation): *Mang cao, chuan xiong, ku shen, dang gui, shuo diao, xi xin, fu zi, da ji, yuan hua, hua jiao, zhi zhu hua, zhu zhi, chi shao*	
		Variant C (1 citation): *Mang cao, chuan xiong, dang gui, shuo diao, xi xin, fu zi, da ji, yuan hua, hua jiao, zhi zhu hua, zhu zhi, chi shao*	
Shuo diao gao	Topical	*Shuo diao, fang feng, bai zhi, jiu, ku shen, sheng ma, she chuang zi, yin yu, du huo, fu zi, xi jiao, mang cao, hua jiao, zhu zhi , ji li, zhi shi, chong wei zi, qiang wei gen, fang ji, mu xiang, she xian cao, bai lian, ji ji*	5
Liu zhi tang xi fang	Topical	*Liu zhi, yin chen, ku shen, lang ya cao, qing xiang ye, tao zhi, huai bai pi, shuo diao, ma huang, yan, mang xiao*	3
Yin yu tang yu fang	Topical	*Yin yu, fang feng, fu zi, mu li, mang cao*	3
Ye ge gao fang	Topical	*Ye ge, niu li zi bing gen, fu zi, cu, zhu zhi*	3

Frequently Used Herbs in Possible Urticaria Citations

A total of 296 herbs were identified in possible urticaria citations (533 citations). Most herbs (223 herbs) were used orally and 135 herbs were indicated for topical use. Some herbs were used both orally and topically. The most frequently reported herbs for oral and topical use are presented separately. *Gan cao* 甘草 was the most frequently cited herb for oral use (see Table 4.8), while *shuo diao* 蒴藋 was most frequently cited herb for topical use (see Table 4.9). Several herbs could be used both orally and topically, including *fang feng* 防风, *chuan xiong* 川芎, *jiu* 酒, *ku shen* 苦参 and *dang gui* 当归.

Table 4.8: Oral Herbs Frequently Used in Possible Urticaria Citations

Herb name	Scientific name	Citation frequency n
Gan cao 甘草	*Glycyrrhiza spp*	151
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	141
Jing jie 荆芥	*Schizonepeta tenuifolia* Briq.	112
Chuan xiong 川芎	*Ligusticum chuangxiong* Hort.	98
Qiang huo 羌活	*Notopterygium spp*	87
Ren shen 人参	*Panax ginseng* C. A. Mey.	87
Fu ling 茯苓	*Poria cocos* (Schw.) Wolf.	75
Zhi ke 枳壳	*Citrus aurantium* L. (dried fruit)	72
Jiu 酒	Wine	71
Chan tui 蝉蜕	*Cryptotympana pustulata* Fabricius.	63
Ku shen 苦参	*Sophora flavescens* Ait.	50
Jiang can 僵蚕	*Bombyx mori* Linnaeus. or *Beauveria bassiana* (Bals.)	50
Chen pi 陈皮	*Citrus reticulata* Blanco.	48
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	46
Hou po 厚朴	*Magnolia officinalis spp*	43
Bai ji li 白蒺藜	*Tribulus terrestris* L. (dried fruit)	42
Huo xiang 藿香	*Pogostemon cablin* (Blanco) Benth. or *Agastache rugosa* (Fisch. & Mey.) O. Ktze.	38
Bo he 薄荷	*Mentha haplocalyx* Briq.	37
Niu bang zi 牛蒡子	*Arctium lappa* L.	36
Man jing zi 蔓荆子	*Vitex trifolia spp*	34

Table 4.9: Topical Herbs Frequently Used in Possible Urticaria Citations

Herb name	Scientific name	Citation frequency n
Shuo diao 蒴藋	*Sambucus javanica* Reinw.	29
Ku shen 苦参	*Sophora flavescens* Ait.	27
Fu zi 附子	*Aconitum carmichaelii* Debx.	26
Feng xiang zhi 枫香脂	*Liquidambar formosana* Hance.	25
Hua jiao 花椒	*Zanthoxylum spp*	21
Zhu zhi 猪脂	Fat	20
Mang cao 莽草	*Illicium lanceolatum* A.C. Smith.	19
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	18
Jiu 酒	Wine	18
Bai fan 白矾	Potassium aluminium sulphate	18

Chuan xiong 川芎	*Ligusticum chuangxiong* Hort.	16
Bai zhi 白芷	*Angelica dahurica spp*	16
Xi xin 细辛	*Asarum spp*	16
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	15
Yuan hua 芫花	*Daphne genkwa* Sieb. et Zucc.	14
Chong wei zi 茺蔚子	*Leonurus japonicus* Houtt.	13
Can sha 蚕沙	*Bombyx mori* L.	13
Mang xiao 芒硝	Hydrated sodium sulphate	12
Yin yu 茵芋	*Skimmia reevesiana* Fortune.	12

Frequently Used Formulae in Most Likely Urticaria Citations

In total, 15 formulae were cited in the 29 most likely urticaria citations. Eleven citations named multi-herb formulae identified for oral use. *Qiang huo dang gui san* 羌活当归散 was the most frequently used oral formula to treat urticaria, as cited in 12 citations (see Table 4.10). This formula could be used on its own to treat wheals and pruritus or in combination with modified *Xiao yao san* 加味逍遥散 or *Bu zhong yi qi tang* 补中益气汤. While the herbs used in these formulae were not specified with symptom descriptions, they were identified from another section of the same classical book. Four topically used formulae were found with three single-herb formulae, including *bai bu* 百部 (three citations), *bi yi tang* 筚衣汤 (two citations) and *xian zi* 蚬子 (one citation). Only one multi-herb formula was applied topically, which was unnamed.

Table 4.10: Oral Formulae Frequently Used in Most Likely Urticaria Citations

Herbal formulae	**Herb ingredients**	**Citation frequency n**
Qiang huo dang gui san	*Qiang huo, dang gui, chuan xiong, huang lian, niu bang zi, fang feng, jing jie, gan cao, huang qin, lian qiao, bai zhi, sheng ma*	4
Qiang huo dang gui san + Jia wei xiao yao san	*Qiang huo, dang gui, chuan xiong, huang lian, niu bang zi, fang feng, jing jie, gan cao, huang qin, lian qiao, bai zhi, sheng ma, gou teng, shao yao, fu ling, bai zhu, chai hu, mu dan pi, shan zhi zi*	4
Qiang huo dang gui	*Qiang huo, dang gui, chuan xiong, huang lian, niu*	4

san + Bu zhong yi qi tang	*bang zi, fang feng, jing jie, gan cao, huang qin, lian qiao, bai zhi, sheng ma, shan zhi zi, gou teng, huang qi, ren shen, bai zhu, zhi gan cao, dang gui, chen pi, sheng ma, chai hu, sheng jiang, da zao*	
Qin jiao niu bang tang	*Qin jiao, niu bang zi, ma huang, ling yang jiao, zhi ke, huang qin, sheng ma, fang feng, gan cao, xuan shen*	2
Dang gui yin	*Dang gui, sheng di huang, chi shao, chuan xiong, jing jie, fang feng, bai zhi, ji li, shou wu, huang qi, gan cao, jiu*	2

Frequently Used Herbs in Most Likely Urticaria Citations

Among the most likely urticaria citations, oral CHM treatments were described in 21 citations, while topical treatments appeared in seven citations. In one citation, the administration method was unclear due to the absence of a description. *Sheng ma* 升麻 became the most frequently cited herb for oral use (18 citations) out of all citations (see Table 4.11). This replaced *gan cao* 甘草 as the most frequently cited herb. However, several key herbs were consistent with those reported in all citations, such as *gan cao* 甘草, *dang gui* 当归 and *jing jie* 荆芥. *Bai bu* 百部 and *jiu* 酒 were the most commonly applied topical herbs (see Table 4.12).

Table 4.11: Oral Herbs Frequently Used in Most Likely Urticaria Citations

Herb name	**Scientific name**	**Citation frequency n**
Sheng ma 升麻	*Cimicifuga spp*	18
Gan cao 甘草	*Glycyrrhiza spp*	17
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	17
Jing jie 荆芥	*Schizonepeta tenuifolia* Briq.	14
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	14
Chuan xiong 川芎	*Ligusticum chuangxiong* Hort.	13
Qiang huo 羌活	*Notopterygium spp*	13
Bai zhi 白芷	*Angelica dahurica spp*	13
Huang lian 黄连	*Coptis spp*	13
Huang qin 黄芩	*Scutellaria baicalensis* Georgi.	12
Lian qiao 连翘	*Forsythia suspensa* (Thunb.) Vahl.	12
Niu bang zi 牛蒡子	*Arctium lappa* L.	9

Gou teng 钩藤	*Uncaria spp*	8
Chai hu 柴胡	*Bupleurum spp*	5
Ren shen 人参	*Panax ginseng* C. A. Mey.	5
Bai zhu 白朮	*Atractylodes macrocephala* Koidz.	4
Huang qi 黄芪	*Astragalus spp*	4
Chen pi 陈皮	*Citrus reticulata* Blanco.	4
Sheng jiang 生姜	*Zingiber officinale* Rosc.	4
Da zao 大枣	*Ziziphus jujuba* Mill.	4

Table 4.12: Topical Herbs Frequently Used in Most Likely Urticaria Citations

Herb name	**Scientific name**	**Citation frequency n**
Bai bu 百部	*Stemona spp*	3
Jiu 酒	Wine	3
Chui fan bi yi 炊饭箅衣	[Scientific name not able to identified]	2

4.3.4 Summary

The greatest number of classical citations was produced by the search term '*yin zhen* 1 瘾疹'. It was also the most commonly observed term in the most likely urticaria citations. The term '*yin zhen* 1 瘾疹' is still used to represent urticaria in contemporary literature (current clinical textbooks and guidelines) (see Chapter 3). As citations containing *feng cheng ge da* 风乘疙瘩 were found only in most likely urticaria citations, this suggests that *feng cheng ge da* 风乘疙瘩 could be closely corresponded to urticaria in ancient times.

Among all citations, *Xiao feng san* 消风散 was the most frequently used formula. As the citations containing *Xiao feng san* 消风散 failed to describe wheals, *Xiao feng san* 消风散 did not appear in the citations that were most likely related to urticaria. In the citations with the richest description of wheals and pruritus (most likely urticaria citations), the most commonly observed formulae were *Qiang huo dang gui san* 羌活当归散, *Qiang huo dang*

gui san 羌活当归散 plus *Jia wei xiao yao san* 加味逍遥散, and *Qiang huo dang gui san* 羌活当归散 plus *Bu zhong yi qi tang* 补中益气汤. None of these three formulae are recommended in contemporary literature. Due to the limited information included in the citations, the reason for this remains uncertain.

Many of the most commonly reported herbs were included in the most frequently cited formulae, such as *Xiao feng san* 消风散, *Mang cao gao* 莽草膏 and *Qiang huo dang gui san* 羌活当归散. These herbs could be categorised as expelling wind and relieving exterior (*jing jie* 荆芥, *fang feng* 防风), dispersing external wind to stop itch (*niu bang zi* 牛蒡子, *chan tui* 蝉蜕, *jiang can* 僵蚕, *bai ji li* 白蒺藜), dispelling wind and removing dampness (*qiang huo* 羌活), tonifying Spleen *qi* and draining dampness (*fu ling* 茯苓, *chen pi* 陈皮, *hou po* 厚朴), and invigorating the Blood (*dang gui* 当归, *chuan xiong* 川芎).

The most frequently reported herb, *gan cao* 甘草, was commonly used to harmonise formulae and had other actions relevant to skin conditions, including tonifying the Spleen and clearing heat. It possesses steroid-like effects, which are useful in the treatment of chronic skin conditions such as urticaria (85). The above herbs are still used in contemporary clinical practice, suggesting little has changed over time in the understanding of urticaria aetiology.

Several herbs could be used both orally and topically, including *fang feng* 防风, *chuan xiong* 川芎, *jiu* 酒, *ku shen* 苦参 and *dang gui* 当归. This suggests that these herbs could relieve symptoms regardless of administration method. Many herbs were not commonly found in current clinical guidelines and textbooks, including *sheng ma* 升麻 for oral use, and *shuo diao* 蒴藋, *feng xiang zhi* 枫香脂, *mang cao* 莽草, *chong wei zi* 茺蔚子 and *yin yu* 茵芋 for topical use. *Sheng ma* 升麻 releases the exterior and disperses heat, promoting eruption and

resolving toxicity, which is beneficial for relieving skin rashes, including wheals (86). *Shuo diao* 蒴藋, *mang cao* 莽草 and *yin yu* 茵芋 expel wind and remove dampness. *Feng xiang zhi* 枫香脂 and *chong wei zi* 茺蔚子 could be used to invigorate the Blood. As current clinical guidelines and textbooks place greater emphasis on oral CHM rather than topical CHM, these topically used herbs were not identified. It was uncertain whether they might be still used in current practice based on practitioners' preference or experience.

4.4 Results of Psoriasis Vulgaris

4.4.1 Characteristics of Citations

The search of the *ZHYD* identified 655 instances of 13 search terms (see Table 4.13). The greatest number of hits was produced by the search term '*feng xuan* 风癣' (301 hits, 46.0%). Search terms '*gou pi xuan* 狗皮癣', '*bai ke chuang* 白壳疮', '*bi feng* 疕风', '*she feng* 蛇风', '*song pi xuan* 松皮癣' and '*yin qian fen*g 银钱疯' accounted for less than one per cent of all hits, which indicated these terms were not commonly observed in classical terminology.

Table 4.13: Hit Frequency by Search Term for Psoriasis Vulgaris

Pinyin	**Chinese characters**	**Citation frequency n (%)**
Feng xuan	风癣	301 (46.0)
Gan xuan	干癣	108 (16.5)
Niu pi xuan	牛皮癣	104 (15.9)
Bai xuan	白癣	57 (8.7)
Bai bi	白疕	29 (4.4)
Gou xuan	狗癣	16 (2.4)
She shi	蛇虱	16 (2.4)
Bai ke chuang	白壳疮	6 (0.9)
Gou pi xuan	狗皮癣	6 (0.9)
She feng	蛇风	4 (0.6)
Song pi xuan	松皮癣	4 (0.6)
Bi feng	疕风	2 (0.3)
Yin qian feng	银钱疯	2 (0.3)

After excluding duplicate citations and those irrelevant to psoriasis vulgaris, 530 citations considered related to CHM for psoriasis were retained. According to pre-defined criteria, each citation was evaluated to select 'possible' or 'most likely' psoriasis vulgaris citations for further analysis. Based on the overall judgment, 68 'possible' and 60 'most likely' psoriasis citations were included.

Eight terms were used to identify citations of psoriasis vulgaris in the 60 most likely psoriasis vulgaris citations: '*bai bi* 白疕' (29 citations), '*gan xuan* 干癣' (28 citations), '*she shi* 蛇虱' (16 citations), '*feng xuan* 风癣' (nine citations), '*she feng* 蛇风' (two citations), '*bi feng* 疕风' (two citations), '*bai ke chuang* 白壳疮' (one citation) and '*bai xuan* 白癣'(one citation). Several citations contained more than one term. All citations containing '*bai bi* 白疕', '*she shi* 蛇虱' and '*bi feng* 疕风' were considered most likely to be related to psoriasis vulgaris. The earliest citation possibly related to psoriasis vulgaris treatment appeared in *Zhu bing yuan hou lun* 诸病源候论 (610 AD), while the most recent one was sourced from *Wai ke shi san fang kao* 外科十三方考 (1947 AD).

4.4.2 Representative Citations

In *Wai ke zheng zhi quan shu* 外科证治全书 (1831) written by Xu Kechang, the symptoms, aetiology and treatments of *bai bi* 白疕 were described:

> *Bai bi* is also called *bi feng*, featuring dry and itchy skin. It looks like rash but with white colour. Scales occur after scratching. The skin will become cracked and bleeding with pain over time due to dryness and lack of nourishment. It will be difficult to scratch as the skin among the 10 fingers become thick. The disease is caused by excess dryness in late autumn. People with Blood deficiency and thin body shape tend to suffer this disease. *Sheng xue run fu yin* can be used orally, and *Zhu zhi* can be applied topically. 清•许克昌《外科证治全书》(1831) 白疕（一名疕风）皮肤燥痒，起如疹疥而色白，搔之屑起，渐至肢体枯燥坼裂，血出痛楚，十指间皮厚而莫能搔痒。因岁金太过，至秋深燥金用事，乃得此证。多患于血虚体瘦之人，① 生血润肤饮主之，②用生猪脂搽之。.

Xu pointed out that internal Blood deficiency and external dryness could trigger *bai bi* 白疕 easily. This was similar to syndrome Blood deficiency and wind-dryness mentioned in contemporary literature (see Chapter 3).

4.4.3 Frequently Used Formulae and Herbs

Frequently Used Formulae in Possible Psoriasis Vulgaris Citations

In the possible psoriasis citations, 27 named herbal formulae were identified, with 10 for oral use and 17 for topical use. The most frequently cited formulae and their ingredients are presented in Tables 4.14 and 4.15. *Sou feng shun qi wan* 搜风顺气丸 was the most frequently cited formula for oral use, reported in five citations (see Table 4.14). The earliest citation of this formula was from *Wai ke zheng zong* 外科正宗 (1,617 AD). *Bai bu gao* 百部膏 was the most commonly reported formula for topical use, cited in *Yi xue xin wu* 医学心悟 (1,732 AD) (see Table 4.15).

Table 4.14: Oral Formulae Frequently Used in Possible Psoriasis Vulgaris Citations

Formula name	**Herb ingredients**	**Citation frequency n**
Sou feng shun qi wan	*Da huang*, *jiu*, *shan yao*, *da zao*, *niu xi*, *tu si zi*, *zhi ke*, *yu li ren*, *qiang huo*, *fang feng*, *du huo*, *che qian zi*, *bing lang*, *feng mi*	5
Fang feng tong sheng san	*Fang feng*, *chuan xiong*, *dang gui*, *shao yao*, *da huang*, *bo he*, *ma huang*, *lian qiao*, *mang xiao*, *shi gao*, *huang qin*, *jie geng*, *hua shi*, *gan cao*, *jing jie*, *bai zhu*, *zhi zi*	3
Ku shen wan	*Ku shen*, *zao jiao*	2
La fan wan	*Huang la*, *ming fan*, *zhu sha*	2
Zhu shen san	*Fu zi*, *jiao hong*, *zhu shen*, *yan*	2

Table 4.15: Topical Formulae Frequently Used in Possible Psoriasis Vulgaris Citations

Formula name	**Herb ingredients**	**Citation frequency n**
Bai bu gao	*Bai bu*, *bai xian pi*, *bi ma zi*, *he shi*, *huang bo*, *dang gui*, *sheng di huang*, *huang la*, *xiong huang*, *ma you*	3
Fu zi san	*Fu zi*, *liu huang*, *cang er zi*	2
Yi mo san	*Tian nan xing*, *cao wu tou*, *yang ti gen*	2
Hai ai tang	*Ai cao*, *ju hua*, *bo he*, *fang feng*, *gao ben*, *huo xiang*, *gan song*, *man jing zi*, *jing jie sui*	2
Yi sao guang	*Ku shen*, *huang bo*, *da feng zi*, *mu bie*, *she chuang zi*, *diao yang chen*, *ku fan*, *xiong huang*, *hua jiao*, *liu huang*, *zhang nao*, *qing fen*, *zhu you*	2

Frequently Used Herbs in Possible Psoriasis Vulgaris Citations

In total, 65 herbs were used orally and 75 herbs were applied topically in possible psoriasis citations. The most commonly reported herbs for oral and topical use are presented separately (see Tables 4.16 and 4.17). *Da huang* 大黄 was the most frequently cited herb for oral use (see Table 4.16), while *wu tou* 乌头 was the most frequently cited herb for topical use (see Table 4.17). Several herbs were used both orally and topically, including *fang feng* 防风, and *dang gui* 当归.

Table 4.16: Oral Herbs Frequently Used in Possible Psoriasis Vulgaris Citations

Herb name	Scientific name	Citation frequency n
Da huang 大黄	*Rheum officinale* Baill.	10
Chen jiu 酒	Wine	10
Feng mi 蜂蜜	*Apis cerana* Fabricius.	9
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	8
Yu li ren 郁李仁	*Prunus japonica* Thunb.	7
Qiang huo 羌活	*Notopterygium spp*	7
Zhi shi 枳实	*Citrus aurantium* L.	7
Huo ma ren 火麻仁	*Cannabis sativa* L.	7
Tu si zi 菟丝子	*Cuscuta chinensis* Lam.	7
Du huo 独活	*Angelica pubescens* Maxim. f. *biserrata* Shan et Yuan.	6
Che qian zi 车前子	*Plantago asiatica* L.	6
Niu xi 牛膝	*Cyathula officinalis* Kuan.	6
Bing lang 槟榔	*Areca catechu* L.	6
Shan zhu yu 山茱萸	*Cornus officinalis Sieb.* et Zucc.	6
Shan yao 山药	*Dioscorea opposita* Thunb.	6
Huang qin 黄芩	*Scutellaria baicalensis* Georgi.	5
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	5
Zhi zi 栀子	*Gardenia jasminoides* Ellis.	4
Chuan xiong 川芎	*Ligusticum chuangxiong* Hort.	4
Bai shao 白芍	*Paeonia lactiflora* Pall.	4

Table 4.17: Topical Herbs Frequently Used in Possible Psoriasis Vulgaris Citations

Herb name	Scientific name	Citation frequency n
Wu tou 乌头	*Aconitum carmichaelii* Debx.	13
Zhu you 猪油	Pig fat	9
Cu 醋	Vinegar	8
(Shi) liu huang (石)硫黄	Sulphur	7
Ban mao 斑蝥	*Mylabris phalerata* Pallas.	7
Yang ti gen 羊蹄根	*Rumex japonicus* Meisn.	7
Huang bo 黄柏	*Phellodendron chinense* Schneid.	5
Xiong huang 雄黄	Arsenic disulphide	5
Zao jiao 皂角	*Gleditsia sinensis* Lam.	5
Bai fan 白矾	Potassium aluminium sulphate	5
She chuang zi 蛇床子	*Cnidium monnieri* (L.) Cuss.	5
Bi ma zi 蓖麻子	*Ricinus communis* L.	5
Huang lian 黄连	*Coptis chinensis* Franch.	4
Shui yin fen 水银粉	[Scientific name not able to be identified]	4
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	4
Jin tuo 津唾	Saliva	4
Huang la 黄蜡	[Scientific name not able to be identified]	4
Xing ren 杏仁	*Prunus armeniaca* L.	3
Tian nan xing 天南星	*Arisaema erubescens* (Wall.) Schott.	3
Hua jiao 花椒	*Zanthoxylum bungeanum* Maxim.	3
Bai xian pi 白鲜皮	*Dictamnus dasycarpus* Turcz.	3
Gao ben 藁本	*Ligusticum sinense* Oliv.	3
Quan xie 全蝎	*Buthus martensii* Karsch.	3
Wu zhu yu 吴茱萸	*Euodia rutaecarpa* (Juss.) Benth.	3
Bo he 薄荷	*Mentha haplocalyx* Briq.	3
Qian dan 铅丹	[Scientific name not able to be identified]	3
Zhang nao 樟脑	*Cinnamomum camphora* (L.) Presl Laurus camphora L.	3
Di huang 地黄	*Rehmannia glutinosa* Libosch.	3
He shi 鹤虱	*Carpesium abrotanoides* L.	3
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	3
Ma you 麻油	Sesame oil	3
Bai bu 百部	*Stemona sessilifolia* (Miq.) Miq.	3

Frequently Used Formulae in Most Likely Psoriasis Vulgaris Citations

Among the 60 most likely psoriasis citations, seven formulae were defined as for oral use, while 15 were designated for topical use. The most frequently cited formulae and their ingredients are presented in Tables 4.18 and 4.19. The formulae list for oral use is consistent with those in possible psoriasis citations. In line with the possible psoriasis citations, *Sou feng shun qi wan* 搜风顺气丸 was the most frequently cited formula for oral use. The formulae list for topical applications in most likely psoriasis citations was slightly different to that of possible psoriasis citations. *Fu zi san* 附子散 was the most frequently reported formula for topical application, described in *Sheng ji zong lu* 圣济总录 (1,117 AD).

Table 4.18: Oral Formulae Frequently Used in Most Likely Psoriasis Vulgaris Citations

Formula name	Herb ingredients	Citation frequency n
Sou feng shun qi wan	*Da huang*, *jiu*, *shan yao*, *da zao*, *niu xi*, *tu si zi*, *zhi ke*, *yu li ren*, *qiang huo*, *fang feng*, *du huo*, *che qian zi*, *bing lang*, *feng mi*	5
Fang feng tong sheng san	*Fang feng*, *chuan xiong*, *dang gui*, *shao yao*, *da huang*, *bo he*, *ma huang*, *lian qiao*, mang xiao, *shi gao*, *huang qin*, *jie geng*, *hua shi*, *gan cao*, *jing jie*, *bai zhu*, *zhi zi*	3
Ku shen wan	*Ku shen*, *zao jiao*	2
La fan wan	*Huang la*, *ming fan*, *zhu sha*	2
Zhu shen san	*Fu zi*, *jiao hong*, *zhu shen*, *yan*	2

Table 4.19: Topical Formulae Frequently Used in Most Likely Psoriasis Vulgaris Citations

Formula name	Herb ingredients	Citation frequency n
Fu zi san	*Fu zi*, *liu huang*, *cang er zi*	2
Jiang can san	*Man jing zi*, *huang qi*, *fu ling*, *ren shen*, *tian nan xing*, *tian ma*, *jiang can*, *du huo*, *qiang huo*, *ge gen*, *gan cao*, *jing jie*, etc.	2
Yi mo san	*Tian nan xing*, *cao wu tou*, *yang ti gen*	2
Hai ai tang	*Ai cao*, *ju hua*, *bo he*, *fang feng*, *gao ben*, *huo xiang*, *gan song*, *man jing zi*, *jing jie sui*	2

Frequently Reported Herbs in Most Likely Psoriasis Vulgaris Citations

The most frequently reported herbs for oral use in most likely psoriasis citations were completely consistent with those in possible psoriasis citations (see Table 4.20). In terms of topical application, the herb list also overlapped with the list for possible psoriasis citations. For instance, the top three herbs were *wu tou* 乌头, *zhu you* 猪油 and *cu* 醋 (see Table 4.21).

Table 4.20: Oral Herbs Frequently Used in Most Likely Psoriasis Vulgaris Citations

Herb name	Scientific name	Citation frequency n
Da huang 大黄	*Rheum officinale* Baill.	10
Chen jiu 酒	Wine	10
Feng mi 蜂蜜	*Apis cerana* Fabricius.	9
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	8
Yu li ren 郁李仁	*Prunus japonica* Thunb.	7
Qiang huo 羌活	*Notopterygium spp*	7
Zhi shi 枳实	*Citrus aurantium* L.	7
Huo ma ren 火麻仁	*Cannabis sativa* L.	7
Tu si zi 菟丝子	*Cuscuta chinensis* Lam.	7
Du huo 独活	*Angelica pubescens* Maxim. f. *biserrata* Shan et Yuan.	6
Che qian zi 车前子	*Plantago asiatica* L.	6
Niu xi 牛膝	*Cyathula officinalis* Kuan.	6
Bing lang 槟榔	*Areca catechu* L.	6
Shan zhu yu 山茱萸	*Cornus officinalis* Sieb. et Zucc.	6
Shan yao 山药	*Dioscorea opposita* Thunb.	6
Huang qin 黄芩	*Scutellaria baicalensis* Georgi.	5
Dang gui 当归	*Angelica sinensis* (Oliv.) Diels.	5
Zhi zi 栀子	*Gardenia jasminoides* Ellis.	4
Chuan xiong 川芎	*Ligusticum chuangxiong* Hort.	4
Bai shao 白芍	*Paeonia lactiflora* Pall.	4

Table 4.21: Topical Herbs Frequently Used in Most Likely Psoriasis Vulgaris Citations

Herb name	Scientific name	Citation frequency n
Wu tou 乌头	*Aconitum carmichaelii* Debx.	13
Zhu you 猪油	Pig fat	9
Cu 醋	Vinegar	8
Ban mao 斑蝥	*Mylabris phalerata* Pallas.	6
Yang ti gen 羊蹄根	*Rumex japonicus* Meisn.	6
(Shi) liu huang (石)硫黄	Sulphur	5
She chuang zi 蛇床子	*Cnidium monnieri* (L.) Cuss.	5
Huang lian 黄连	*Coptis chinensis* Franch.	4
Zao jiao 皂角	*Gleditsia sinensis* Lam.	4
Bai fan 白矾	Potassium aluminium sulphate	4
Shui yin fen 水银粉	[Scientific name not able to be identified]	4
Xing ren 杏仁	*Prunus armeniaca* L.	3
Tian nan xing 天南星	*Arisaema erubescens* (Wall.) Schott.	3
Gao ben 藁本	*Ligusticum sinense* Oliv.	3
Quan xie 全蝎	*Buthus martensii* Karsch.	3
Wu zhu yu 吴茱萸	*Euodia rutaecarpa* (Juss.) Benth.	3
Qian dan 铅丹	[Scientific name not able to be identified]	3
Bo he 薄荷	*Mentha haplocalyx* Briq.	3
Jin tuo 津唾	Saliva	4
Zhang nao 樟脑	*Cinnamomum camphora* (L.) Presl Laurus camphora L.	3
Fang feng 防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	3

4.4.4 Summary

The greatest number of overall classical citations was produced by the search term '*feng xuan* 风癣'. However, after applying symptom and clinical judgment, few citations that were identified by '*feng xuan* 风癣' remained. This suggests that this term could refer to conditions other than psoriasis vulgaris. '*Bai bi* 白疕', '*she shi* 蛇虱' and '*bi feng* 疕风' were

all cited in most likely psoriasis vulgaris citations, indicating these could be the terms that most closely referred to the condition.

It was surprising that the commonly reported formulae in the most likely psoriasis vulgaris citations were not consistent with current clinical practice (see Chapter 3). For instance, the most frequently reported formula, *Sou feng shun qi wan* 搜风顺气丸, promotes *qi* movement and is often used to treat gastrointestinal disease in contemporary practice. Although some herb ingredients of main formulae (*jing jie* 荆芥, *fang feng* 防风 and *huang qi* 黄芪) are still used in modern times, it is uncertain if formulae in current practice originated or were modified from those in classical literature.

The most frequently used herbs for oral use in the most likely psoriasis vulgaris citations could be categorised as clearing heat (*da huang* 大黄, *huang qin* 黄芩 and *zhi zi* 栀子), dispersing external wind (*fang feng* 防风), removing dampness (*qiang huo* 羌活, *du huo* 独活 and *che qian zi* 车前子) and herbs for tonifying (*tu si zi* 菟丝子, *niu xi* 牛膝, *shan zhu yu* 山茱萸, *shan yao* 山药). Blood syndrome herbs were *dang gui* 当归, *chuan xiong* 川芎 and *bai shao* 白芍. These were observed at a lower frequency and were not commonly cited in the classical literature, although they are commonly used in current practice. This might be due to the variation in the environment or historical development of CM etiology of psoriasis vulgaris. External wind invasion was believed to the etiological factor for psoriasis vulgaris in the Sui and Tang dynasties. In the Ming and Qing dynasties, the internal factor of Blood syndrome rose in prominence (87). The treatment principle of psoriasis vulgaris in current clinical practice mainly targets Blood syndromes, especially Blood stasis (see Chapter 3).

Several herbs for topical use in classical citations are still utilised in current clinical practice. For instance, *fang feng* 防风, *she chuang zi* 蛇床子 and *shi liu huang* 石硫黄 are often used

to disperse wind and stop itch; and *huang lian* 黄连 to eliminate heat. *Cu* 醋, *zhu you* (pig fat) 猪油 and *jin tuo* (saliva) 津唾 were used as excipients to bind herbs in classical times, but *jin tuo* (saliva) 津唾 is no longer utilised for health reasons. Due to the toxicity of herbs, *wu tou* 乌头, *ban mao* 斑蝥, *qian dan* 铅丹 and *shui yin* 水银粉 (86) are rarely used in the treatment of psoriasis vulgaris in modern clinical settings.

4.5 Discussion and Conclusion

In current clinical guidelines and textbooks, *Xiao feng san* 消风散 and *Dang gui yin zi* 当归饮子 could be used to treat urticaria and psoriasis vulgaris. Interestingly, *Xiao feng san* 消风散 was most frequently reported in the citations related to urticaria, which suggests *Xiao feng san* 消风散 has stood the test of time and might become a promising formula for the treatment of urticaria. Neither of these formulae were identified in the psoriasis vulgaris classical citations. This might be due to the contemporary clinical practice principle of focusing on Blood syndromes. *Xiao feng san* 消风散 and *Dang gui yin zi* 当归饮子 are currently used for Blood heat and Blood dryness of psoriasis vulgaris.

Other formulae in the citations related to urticaria and psoriasis vulgaris are no longer used in current clinical practice, such as *Qiang huo dang gui san* 羌活当归散 and *Mang cao gao* 莽草膏 for urticaria, and *Sou feng shun qi wan* 搜风顺气丸 for psoriasis vulgaris. This might be due to management of urticaria and psoriasis vulgaris evolving in line with CM etiology for these two conditions. As the information contained in the classical citations is limited, this is an area that needs to be explored in the future research on classical literature.

In the most likely urticaria and psoriasis vulgaris citations, the CHM treatments for these two conditions had several herbs in common, including *fang feng* 防风, *jing jie* 荆芥, *gan cao* 甘

草, *qiang huo* 羌活, *dang gui* 当归 and *chuan xiong* 川芎. This suggests similarities in the treatments of urticaria and psoriasis vulgaris in classical literature. It should be noted that *gan cao* 甘草 was the most frequently used herb for urticaria in classical works. *Gan cao* 甘草 can harmonise ingredients in a formula, but also has steroid-like effects (85, 86), which could be used to treat skin conditions, including urticaria and psoriasis. While *gan cao* 甘草 was not the most frequently cited in the classical psoriasis citations, the commercial products extracted from *gan cao* 甘草 have been used in current clinical practice (85).

Although the *ZHYD* is a comprehensive collection of a wide range of books across multiple eras, it does not encompass all classical books since classical literature was vast. In addition, the search terms used for the *ZHYD* might not be comprehensive enough to return all relevant citations. Only 68 citations related to psoriasis vulgaris were found. Therefore, formulae used in current practice were not identified in classical literature.

The formulae and herbs identified in classical literature can be taken into consideration when prescribing formulae for these two conditions in contemporary clinical practice. The efficacy and safety of the less frequently used herbs or formulae in current practice should be evaluated through experimental and clinical studies.

Chapter 5. Methods for Evaluating Clinical Evidence of Chinese Herbal Medicine for Chronic Urticaria and Psoriasis Vulgaris

5.1 Introduction

Clinical evidence refers to information gathered from various types of studies, such as SRs, RCTs, CCTs, case reports and case-series studies (non-controlled studies). SRs are deemed the highest level of clinical evidence (88). According to a pre-defined review protocol, SRs synthesise clinical evidence through systematic search and evaluation of methodology quality. SRs could answer specific clinical and research questions, and assist clinical decision-making and healthcare policymakers (89). As a world leader in SR methodology, the Cochrane Collaboration provides the best available evidence for practitioners, researchers and policymakers. Following the rigorous methodology provided by the Cochrane Collaboration, three SRs were conducted to gather and summarise clinical evidence of CHM for chronic urticaria and psoriasis vulgaris. All three review protocols have been registered in PROSPERO (see Chapters 6, 7 and 8 for PROSPERO registration numbers). This chapter describes the general methods used to evaluate clinical evidence. The overall procedures are the same for all SRs. Inclusion criteria of the included studies differed in SRs due to the diversity of chronic urticaria and psoriasis vulgaris.

5.2 Inclusion Criteria

5.2.1 Chronic Urticaria

5.2.1.1 Types of Study

RCTs on CHM for people with chronic urticaria were included. Non-randomised CCTs, non-controlled studies and experimental studies were excluded.

5.2.1.2 Participants

People with chronic urticaria were considered regardless of subtypes because clinical management is the same for spontaneous and inducible urticarias. Chronic urticaria was defined as the occurrence of hives and/or angioedema for six weeks or longer (8, 10).

5.2.1.3 Interventions

Any forms of CHM alone or in combination with conventional therapies were accepted. The administration of CHM included oral decoction, capsule, granule and topical application alone, or the combination of various preparation types. Studies employing conventional therapies as co-interventions were included. The conventional therapies were consistent with those in the control group. Studies that used other CM therapies (for example, acupuncture) as co-interventions were excluded.

5.2.1.4 Comparators

Studies using the following comparators were considered: placebo, no treatment or conventional therapies. Conventional therapies were limited to those recommended in international clinical practice guidelines (for example, non-sedating second-generation H1 antihistamines, omalizumab and ciclosporin A) for chronic urticaria (8, 10, 11).

5.2.1.5 Outcomes

All pre-specified outcomes were clinically oriented, including those recognised internationally and used in China most commonly, such as effective rate (ER) based on symptoms (see Table 5.1). Disease activity was measured by three outcomes: Urticaria Activity Score (UAS) (0–6 points)/UAS7 (0–42 points) (10), Urticaria Severity Score (USS)

(0–93 points) (90), and Urticaria Control Test (UCT) (0–16 points) (91). For all outcomes, a lower score indicated improvement in urticaria symptoms.

Similarly, patients' health-related QoL (HR-QoL) was evaluated using one urticaria-specific outcome measure, Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) (0–100 points) (92), and one general dermatology questionnaire, Dermatology Life Quality Index (DLQI) (0–30 points) (93). Again, a lower score indicated better HR-QoL.

Global assessment of symptoms (effective rate, ER) included two approaches. The first approach followed the *Standard of diagnosis and assessment of treatment effects of dermatological conditions in Chinese medicine* «中医皮肤科病证诊断疗效标准» (63), which describes criteria for improvement in wheals and pruritus. 'ER 30' was defined as the number of people who achieved a 30% (or more) improvement according to the criteria of this approach. The second involved a calculation of change from baseline in symptom scores of wheals and pruritus (with or without other symptoms) (Symptom Severity Reduction Index [SSRI]). The evaluation domains of the scoring systems varied across studies, which included pruritus, quantity and diameter of wheals, oedema-size, dermatographism, frequency or duration of symptoms. A score was allocated to each symptom, from 0 (no symptoms) to 3 or 4 (worst possible symptoms), and the score change was calculated. SSRI 30 was defined as the number of people who achieved a 30% (or higher) score change. As no consensus was reached on the ER threshold, SSRI 30 was chosen for the SRs based on criteria described in CM guidelines (63). If the rate of people who achieved a 30% score change was not available, the number of people who achieved more than a 30% score change was used for analysis. In the *Standard of diagnosis and assessment of treatment effects of dermatological conditions in Chinese medicine* «中医皮肤科病证诊断疗效标准» (63), the definition of clinical cure was provided. Therefore, the relapse rates based on this guideline were also evaluated.

Table 5.1: Pre-specified Outcomes for Systematic Reviews of Chronic Urticaria

Outcome categories	Outcome measures
Disease activity	Urticaria Activity Score (UAS)/UAS7
	Urticaria Severity Score (USS)
	Urticaria Control Test (UCT)
Health-related quality of life (HR-QoL)	Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)
	Dermatology Life Quality Index (DLQI)
Effective rate	Effective rate (ER 30): 30% or greater improvement in wheals and pruritus
	Symptom Severity Reduction Index (SSRI 30): 30% or greater change in symptom score from baseline
Relapse rate	Calculated based on ER 30
Adverse events	Number and type of adverse events

5.2.2 Psoriasis Vulgaris

5.2.2.1 Types of Study

RCTs comparing CG plus guidelines recommended conventional therapy with the same conventional therapy alone for psoriasis vulgaris were included (12, 13). CCTs, non-controlled studies and experimental studies were excluded.

5.2.2.2 Participants

People with a diagnosis of psoriasis vulgaris were considered without limitation on psoriasis stages.

5.2.2.3 Interventions

CG, regardless of preparation type, plus international guidelines recommended conventional therapies were used in the intervention group.

5.2.2.4 Comparators

The comparators were conventional therapies that corresponded with those in the intervention group. The conventional therapies included topical therapies (for example, corticosteroids),

phototherapy (narrow-band ultraviolet (UV)-B: NB-UVB) and systemic agents (for example, acitretin) (12, 13).

5.2.2.5 Outcomes

The primary outcome was the proportion of patients achieving a PASI rate of 60 (that is, 60% or greater reduction of PASI score). PASI 60 is recommended in the *Consensus of diagnosis and treatment of psoriasis vulgaris in integrative medicine* 寻常性银屑病中西医结合诊疗共识, published in China (94). Based on international guidelines, PASI 50/75 are considered treatment goals (12, 95). As previous SRs (28, 96) suggested that PASI 60 was frequently used in RCTs in China, PASI 60 was selected as the primary outcome. Secondary outcomes included PASI 90 (clinically cured) measures of HR-QoL (that is, DLQI, relapse rates and AEs).

5.3 Search Strategy

An initial search of English and Chinese databases was conducted for clinical evidence relating to chronic urticaria from inceptions to May 2014, and an update search was performed in July 2015. The five English databases were PubMed, Excepta Medica Database (Embase), Allied and Complementary Medicine Database (AMED), Cumulative Index of Nursing and Allied Health Literature (CINAHL) and Cochrane Central Register of Controlled Trials (CENTRAL). Four Chinese databases were searched: China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP) and Wanfang Databases. Search terms (see Appendix 1) were grouped according to intervention (herbal medicine, CM, CM treatment and variants), condition (urticaria, hives, wheals and variants) and study design (randomly, randomised, controlled and variants).

For psoriasis vulgaris, five English databases (PubMed, Embase, CINAHL, CENTRAL and AMED), one Japanese database (CiNii) and four Chinese databases (CBM, CNKI, CQVIP and Wanfang Database) were searched from inceptions to July 2015. Search terms (see Appendix 2) were grouped according to intervention (glycyrrhizin and variants), condition (psoriasis and variants) and study design (randomly, randomised and variants), with adjustments for each database search.

5.4 Data Collection and Analysis

5.4.1 Selection of Studies

Identified citations were exported to Endnote reference management software for further screening. Through reading titles and abstracts, two reviewers (Jingjie Yu and Yiqi Du for chronic urticaria citations, Jingjie Yu and Claire Zhang for psoriasis vulgaris citations) independently screened the studies against the inclusion criteria. Full-text articles were obtained to ensure potentially relevant citations were included in further evaluation. Any disagreement was resolved through discussion or consultation with the third reviewer (Meaghan Coyle).

5.4.2 Data Extraction

Data from the eligible studies were extracted by two reviewers (Jingjie Yu and Yiqi Du for chronic urticaria studies, Jingjie Yu and Claire Zhang for psoriasis vulgaris studies) independently using a pre-defined Excel form designed by China-Australia International Research Centre for Chinese Medicine (see Appendix 3). The data extraction form covered the details relating to the characteristics of the studies, interventions, comparators and outcomes. For missing or incomplete data, the author of the study was contacted to seek more

detailed information or clarification via email. If additional data or further reply could not be obtained from the authors, the data were excluded from final analysis.

5.4.3 Risk of Bias Assessment

The risk of bias of each included study was independently evaluated by two reviewers (Jingjie Yu and Yiqi Du for chronic urticaria studies, Jingjie Yu and Claire Zhang for psoriasis vulgaris studies) using the Cochrane Collaboration's risk of bias assessment tool (89). The assessment tool for risk of bias contains six domains (see Table 5.2). Each study was assessed as 'low risk of bias', 'unclear' or 'high risk of bias'. Disagreement arising during the assessments was resolved via discussion between the two reviewers. If consensus could not be reached, consultation was made with the third reviewer (Meaghan Coyle).

Table 5.2: Tool for Assessment of Risk of Bias

Bias categories	**Domain**
Selection bias	Random sequence generation
	Allocation concealment
Performance bias	Blinding of participants and personnel
Detection bias	Blinding of outcome assessment
Attrition bias	Incomplete outcome data
Reporting bias	Selective reporting

5.4.4 Statistical Analysis

Data related to CHM formulae and herbs were analysed for frequency of usage using descriptive statistics. The herbal names were standardised according to a nomenclature list of commonly used CHMs (last updated in September 2015) provided by the CMBA. This was done to account for different names of herbs in each study. Moreover, a herb prepared with different processing methods was regarded as the same herb when calculating the frequency. For instance, *zhi gan cao* 炙甘草 is processed through frying *sheng gan cao* 生甘草 with

honey. *Zhi gan cao* 炙甘草 and *sheng gan cao* 生甘草 were merged as *gan cao* 甘草 for analysis. The most frequently used formulae or herbs were presented.

Outcome data were analysed using Review Manager 5.3 software(97). Dichotomous data were reported as risk ratio (RR) and continuous data reported as mean difference (MD), with 95% confidence intervals (CI). To present a clear difference of effects between intervention and comparator, risk difference (RD) was also used in the SR on psoriasis vulgaris. RD was presented as the actual difference in risk between the intervention and control groups. Random or fixed effects analysis was selected, taking into account clinical and statistical heterogeneity. The clinical heterogeneity was considered based on the demographics of participants, and study design, such as allocation concealment, blinding, treatment duration and outcome assessments. Statistical heterogeneity was evaluated using the I^2 statistic. Sensitivity analysis was performed where moderate to substantial statistical heterogeneity was detected (I^2>50%), based on risk of bias for sequence generation. Where possible, subgroup analysis was planned according to characteristics of participants (demographic data), interventions (CHM formula, preparation type) or comparators (dosage, subclass of conventional therapy). Publication bias was explored by visual inspection of funnel plots when a meta-analysis included 10 or more studies.

5.5 Summary

This chapter introduces the general methods used to evaluate the clinical evidence. Clinical evidence was evaluated and synthesised through SRs of RCTs following the rigorous methodology of the Cochrane Collaboration. Up to 10 databases (English, Chinese and Japanese) were searched to identify relevant articles. Three SRs were conducted:

1. CHM alone for chronic urticaria
2. CHM as add-on therapy for chronic urticaria

3. CG for psoriasis vulgaris.

Statistical analyses were performed in Review Manager 5.3.

Chapter 6. Systematic Review 1:

Chinese Herbal Medicine for Chronic Urticaria

6.1 Introduction

Urticaria is defined by the rapid onset of wheals, with or without angio-oedema (10). Wheals are typically accompanied by pruritus and are transient in nature, with the skin returning to its normal appearance in one to 24 hours (8). Acute urticaria is defined as the occurrence of hives and/or angioedema for less than six weeks, while episodes lasting six weeks or longer are regarded as chronic urticaria (8, 10).

According to a representative cross-sectional sample of 13,300 people, the lifetime prevalence rate of urticaria is 8.8% for all types of urticaria and 1.8% for chronic urticaria (9). Chronic urticaria is observed more commonly in women than in men (9, 37). Frequent recurrences have a significant impact, including high economic and health burdens (9, 20). The burden of chronic urticaria on HR-QoL has been estimated as similar to that of coronary artery disease (17).

In approximately 75% of cases, the cause of chronic urticaria is unknown (98). Even when a cause has been identified, it can be difficult to avoid recurrence. Second-generation antihistamines are recommended as first-line therapy for chronic urticaria (8, 10). Second-generation antihistamines are effective in reducing wheals and pruritus and are safe for use (8, 10). Despite demonstrated effect, some patients do not achieve adequate symptom control, or may experience a worsening of symptoms (57).

CAM use among people with skin conditions is common and herbal medicine is becoming a popular option (24–26). To date, no SRs of CHM for chronic urticaria have been published in

English. Three SRs of CHM (32–34) have been identified from the Chinese databases. All SRs concluded that CHM had superior efficacy compared with antihistamines. Among them, two SRs (32, 33) focused on one formula (*Dang gui yin zi* 当归饮子) for chronic urticaria, with narrow inclusion criteria. The reliability of the findings is uncertain due to meta-analysis including data from diverse outcome measures with different outcome criteria. Further, the outcomes were not recognised internationally. The third SR evaluated the efficacy and safety of CHM for chronic urticaria (34). However, only one English database (PubMed) was searched for this SR, and the search of Chinese databases did not include major databases, such as CQVIP. Statistical heterogeneity meant that meta-analysis was not performed. However, the researchers did not explore possible reasons for heterogeneity.

Overall, the evidence on the efficacy and safety of CHM for chronic urticaria from current modern literature is lacking. SRs based on comprehensive searches and rigorous methodology are required to provide solid evidence. The objective of this SR is to evaluate the efficacy and safety of CHM alone for chronic urticaria using rigorous methods.

6.2 Methods

The methods for SR of CHM for chronic urticaria were described in Chapter 5. This review has been registered in PROSPERO (CRD42015027764).

6.3 Results

Extensive database searches revealed 7,631 potentially relevant citations. After removing duplicates, 5,666 records were screened and full texts of 1,925 were retrieved (see Figure 6.1). Twenty-six RCTs met the inclusion criteria. All studies were conducted in China and published in Chinese journals between 2002 and 2015. Two studies adopted a three-arm design (99, 100) and the remaining studies used a two-arm parallel design. In total, 2,761

patients with chronic urticaria were recruited from the outpatient or inpatient departments of hospitals. The sample size of included studies ranged from 55 (101) to 400 (102). Participants' age ranged from six to 70 years (see Table 6.1). Median treatment duration was four weeks, with treatments ranging from 10 days (103) to three months (102). Follow-up assessment was mentioned in 19 studies, which ranged from four weeks to one year (see Table 6.1). All studies except one reported the number of participants suffering relapse (104).

6.3.1 Intervention and Co-intervention/Comparator

CHM were administrated orally as decoction in 21 studies, as granules in three studies (103, 105, 106), as capsules in one study (107) and one study (108) did not report the preparation type (see Table 1). Although CHM formulae were diverse across the studies (see Table 6.2), the most frequently used herbs were *fang feng* 防风 (*Saposhnikovia divaricata* [Turcz.] Schischk.) (19 studies), *gan cao* 甘草 (*Gycyrrhiza spp*) (17 studies), *dang gui* 当归 (*Angelica sinensis* [Oliv.] Diels.) (13 studies), *huang qi* 黄芪 (*Astragalus membranaceus* [Fisch.]) (13 studies) and *jing jie* 荆芥 (*Schizonepeta tenuifolia* Briq.) (13 studies). All studies used second-generation H1-antihistamines as the comparator, most commonly cetirizine, levocetirizine or loratadine. Oral administration of antihistamines was administered in dosages of five milligrams (mg) or 10 mg daily.

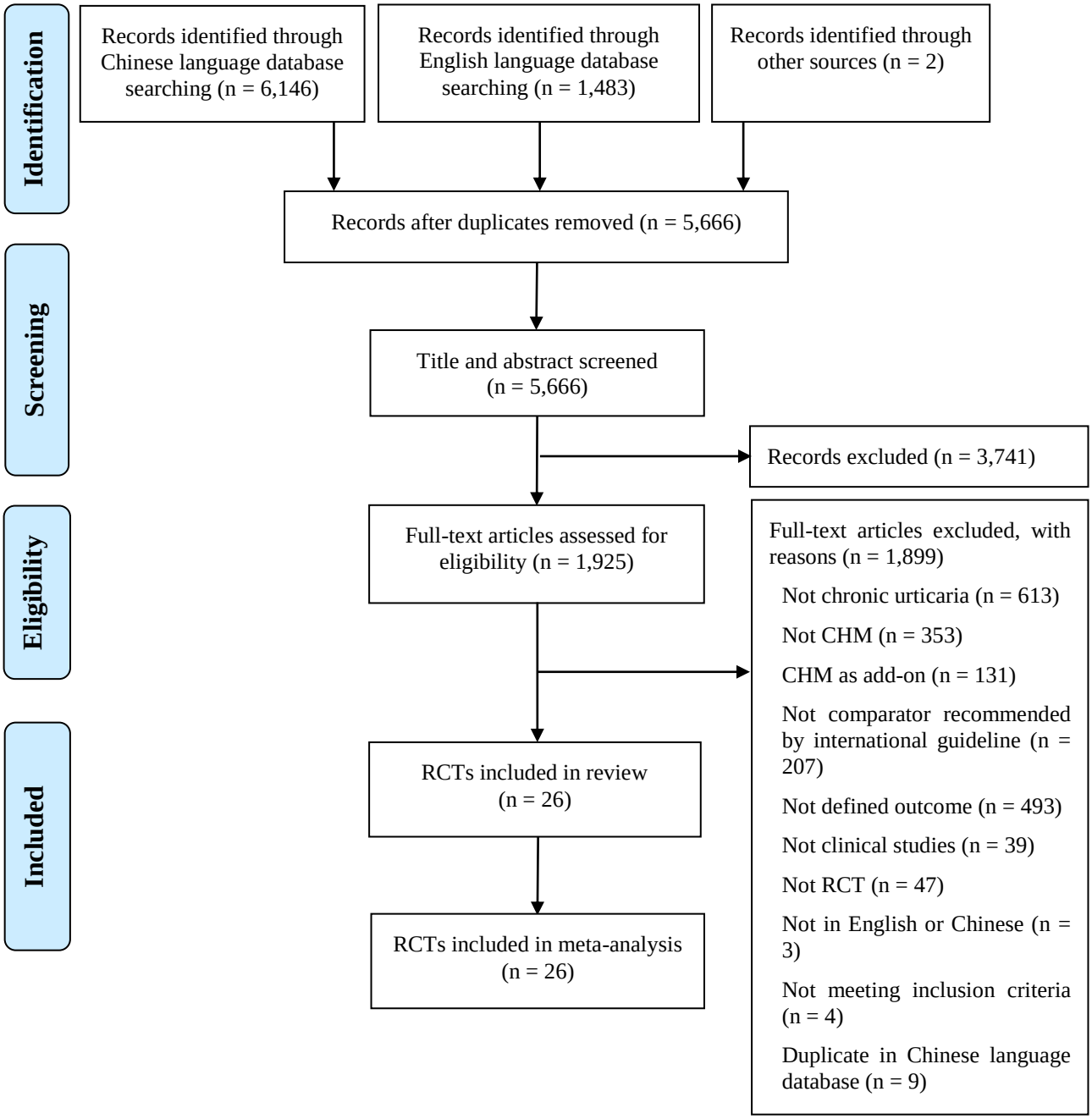

Figure 6.1: PRISMA Flow Chart of Study Selection Process: Chinese Herbal Medicine v. Second-Generation Antihistamines for Chronic Urticaria

Notes: CHM: Chinese herbal medicine; RCT: randomised controlled trial

Table 6.1: Characteristics of Included Randomised Controlled Trials: Chinese Herbal Medicine v. Antihistamines for Chronic Urticaria

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Bian XL 2006 (107)	NS; 2	4 w; 3 m–6m	I: 5.21 y	I: 54/54; 0	I: 41.5 y; 32/22	*Dan long zhi yang jiao nang* (capsule): capsule; four capsules, three times daily	Cetirizine: 10 mg qd, po	NS
			C: 4.83 y	C: 30/30; 0	C: 42 y; 18/12			
Chen H 2009 (109)	NS; 2	4 w; 6 m–1.5y	I: 5 m–12 y	I: 41/41; 0	I: 29.6 (3.2) y; 17/24	*Gui zhi tang* (modified): decoction; twice daily	Loratadine: adults, 10 mg qd, po; children (age<12), 5 mg qd, po	NS
			C: 4 m–10 y	C: 37/37; 0	C: 30.4 (2.8) y; 16/21			
Chen XJ 2009 (101)	NS; 2	4 w; NS	Total: 1–3 y	I: 35/35; 0	Total: 18–65 y; 23/32	*Dang gui yin zi* (modified): decoction; twice daily	Desloratadine dispersible tablets: 5 mg qd, po	NS
				C: 20/20; 0				
Huang N 2011 (110)	NS; 2	4 w; 8 w	I: 5 y	I: 63/63; 0	I: 42 y (14–63 y); 42/21	*Qu shi hua zhi jie du tang*: decoction; three times daily	Levocetirizine: 5 mg daily	None
			C: 6.5 y	C: 63/63; 0	C: 40.5 y (13–59 y); 38/25			

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Jin RJ 2006 (111)	NS; 2	4 w; 12 w	I: 8.2 m	I: 46/46; 0	I: 12–35 y; 22/24	*Wu wei zi tang*: decoction; twice daily	Loratadine tablets: 10 mg qn	I: diarrhoea (4), sick (1)
			C: 8.6 m	C: 40/40; 0	C: 12–40 y; 25/15			C: somnolence (1), hyperphagia (1), dizziness and tired (1)
Kong DY 2015 (105)	NS; 2	4 w; 4 w	I: 1.04 (0.4) y	I: 64/64; 0	I: 26.8 (8.5) y; 33/31	*Yu ping feng san* (modified): granule; twice daily	Levocetirizine dihydrochloride: 5 mg daily	I: gastro discomfort (1), somnolence (2)
			C: 1.05 (0.8) y	C: 64/64; 0	C: 27.2 (6.5) y; 32/32			C: dizziness (5), somnolence (3)
Li AJ 2012 (112)	NS; 2	4 w; 1 y	I: 6 m–4 y	I: 40/40; 0	I: 23.5 (3.5) y; 18/22	*Ma huang fu zi xi xin tang* (modified): decoction; twice daily	Loratadine: 10 mg qd, po	NS
			C: 7 m–5 y	C: 36/36; 0	C: 24.7 (2.9) y; 16/20			

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Li JY 2009 (103)	NS; 2	10-40 d; 6 m	I: 11.3 m	I: 130/130; 0	I: 33.4 y (12–59 y); 63/67	*Kang guo min ke li* (granule): granule; 30 g, twice daily	Cetirizine hydrochloride: 10 mg qd, po	NS
			C: 9.3 m	C: 66/66; 0	C: 36.5 y (15–53 y); 30/36			
Li YB 2013 (102)	NS; 2	3 m; NS	I: 9 m–15 y	I: 300/300; 0	I: 7–58 y; 183/117	*Man xun yin*: decoction; three times daily	Loratadine: one tablet qd, po	NS
			C: 6 m–13 y	C: 100/100; 0	C: 6–57 y; 61/39			
Luo B 2006 (106)	NS; 2	30 d; 3 m	I: 24.6 (41.4) m	I: 80/80; 0	I: 32.1 (17.2) y; 28/52	*Xiao feng zhi yang ke li* (granule): granule; 12g each time, three times daily	Loratadine: 10 mg qn	I: mild diarrhoea (5)
			C: 23.5 (48.1) m	C: 80/80; 0	C: 31.6 (15.4) y; 23/57			C: tired (13), thirsty (4)
Luo MY 2006 (113)	NS; 2	4 w; 3 m	I: 6.35 m	I: 42/42; 0	I: 35.2 y (12 y–58 y); 14/28	*Kang xun tang*: decoction; three times daily	Mizolastine: 10 mg daily	I: none
			C: 6.26 m	C: 38/38; 0	C: 35.7 y (13y–57 y); 11/27			C: somnolence (3), dizziness and tired (2), thirsty (2)

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Shi CR 2013 (99)	NS; 3	28 d; 3 m, 6 m	I: 1.60 (0.56) y	I: 25/21; 4	I: 34.14 (12.64) y; 13/12	*Dang gui yin zi*: decoction; twice daily	C1: Cetirizine hydrochloride: 10 mg daily C2: *Dang gui yin zi*; cetirizine hydrochloride	I: diarrhoea (2)
			C1: 1.50 (0.62) y	C1: 25/24; 1	C1: 36.63 (13.98) y; 12/13			C1: dizziness (1), somnolence (1)
			C2: 1.80 (0.45) y	C2: 25/22; 3	C2: 35.37 (13.54) y; 11/14			C2: none
Wang HL 2010 (104)	NS; 2	36 d; 6 m	I: 3.1 y	I: 60/60; 0	I: 36 y (16–62 y); 34/26	*Ma huang lian qiao chi xiao dou tang*: decoction; twice daily	Cetirizine: 10 mg qd, po	NS
			C: 2.9 y	C: 30/30; 0	C: 34 y (14–66 y); 16/14			
Wang L 2006 (115)	NS; 2	30 d; 3 m	I: 3 m–3 y	I: 52/52; 0	I: 19–54 y; 32/20	*Shu feng chu shi tang*: decoction; twice daily	Loratadine tablets: 10 mg qn	I: diarrhoea (10)
			C: 3 m–2.5 y	C: 52/52; 0	C: 19–55 y; 28/24			C: somnolence (11), hyperphagia (12), dizziness and weak (6)

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Wo LY 2008 (116)	NS; 2	1 m; NS	I: 2–36 m	I: 56/56; 0	I: 11–58 y; 24/32	Investigator-designed formula *Ping min jian* (modified): decoction; NS	Cetirizine hydrochloride: 10 mg daily	NS
			C: 2–38 m	C: 44/44; 0	C: 13–57 y; 15/29			
Wu H 2003 (114)	NS; 2	8 w; NS	Total: 13m–6 y	I: 40/40; 0	Total: 44 y (23–65 y); 28/52	*Yu ping feng guo min jian*: decoction; twice daily	Cetirizine hydrochloride: 10 mg qd, po	NS
Xiao HL 2002 (117)	NS; 2	4 w; 3 m	NS	I: 30/30; 0	I: NS; 12/18	*Dang gui yin zi*: decoction; twice daily	Loratadine: 10 mg qd, po	NS
				C: 30/30; 0	C: NS; 15/15			
Xue CL 2009 (100)	NS; 3	30 d; NS	I: 4.58 y	I: 43/43; 0	I: 24.25 y (8–53) y; 20/23	*Kang man min jian*: decoction; 150 ml, three times daily	C1: Cetirizine: 10 mg, three times daily C2: *Kang man min jian*; cetirizine	NS
			C1: 3.36 y	C1: 45/45; 0	C1: 22.16 y (11–49) y; 23/22			
			C2: 5.24 y	C2: 51/51; 0	C2: 23.74 y (13–57) y; 23/28			
Yan X 2009 (118)	NS; 2	6 w; 6 w	I: 2.77 (1.4) y	I: 34/34; 0	I: 36.87 (12.98) y; 11/23	*Xiao xun fang*: decoction; twice daily	Loratadine: one tablet daily	I: NS
			C: 2.69 (1.32) y	C: 34/34; 0	C: 37.33 (15.56) y; 9/25			C: somnolence, thirst, sick, anepithymia (NS)

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Yang GH 2012 (120)	NS; 2	2 w; NS	I: 2 m–12 y	I: 36/36; 0	I: 18–70 y; 16/20	*Yang zhen tang*: decoction; twice daily	Cetirizine or Mizolastine Sustained-release Tablets: 10 mg daily	I: none
			C: 2.4 m–11 y	C: 36/36; 0	C: 20–69 y; 15/21			C: dry mouth, constipation (NS)
Yang SR 2014 (121)	NS; 2	4 w; 1 m	NS	I: 36/36; 0	I: 39.4 (12.1) y; 17/19	*Ma xing shi gan tang* (modified): decoction; twice daily	Levocetirizine dihydrochloride drops: 10 mg qn	NS
				C: 32/32; 0	C: 38.2 (11.6) y; 16/16			
Yu GH 2009 (119)	NS; 2	1 m; NS	I: 2 m–36 m	I: 52/52; 0	I: 11–58 y; 22/30	Investigator-designed formula *Ping min jian* (modified): decoction; three times daily	Cetirizine hydrochloride: 10 mg daily	NS
			C: 2 m–38 m	C: 44/44; 0	C: 13–57 y; 15/29			
Zhang BX 2013 (123)	NS; 2	4 w; 4 w	I: 7 w–4.5 y	I: 42/42; 0	I: 18–68 y; 17/25	*Mang huang lian qiao chi xiao dou tang* plus *Dang gui yin zi* (modified): decoction; 300 ml twice daily	Levocetirizine dihydrochloride: 5 mg daily	I: loose stool (1)
			C: 8 w–5.3 y	C: 35/35; 0	C:20–66 y; 16/19			C: somnolence, dry mouth (NS)

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Control	Adverse events
Zhang CJ 2011 (108)	NS; 2	4 w; 6 m	NS	I: 76/76; 0	I: NS; NS	*Shu gan huo xue qu feng fang*: NS; NS	Levocetirizine dihydrochloride: 5 mg daily	I: none
				C: 67/67; 0	C: NS; NS			C: dizziness and headache (2), thirsty and tired (1)
Zhang EH 2007 (122)	NS; 2	4 w; 8 w	I: 1.70 (2.59) y	I: 30/30; 0	I: 36.87 (12.98) y; 8/22	*Guo min jian* (modified): decoction; twice daily	Cetirizine hydrochloride: 10 mg qd	I: sick (1)
			C: 1.73 (2.05) y	C: 30/30; 0	C: 37.33 (15.56) y; 11/19			C: somnolence (3), thirsty (1), sick (1), poor appetite (1)
Zhu WR 2011 (124)	NS; 2	4 w; 1 m	I: 2–64 m	I: 30/30; 0	I: 19–60 y; 11/19	*Di shen qu feng he ji* (mixture): decoction;150 ml bid	Loratadine: 10 mg qn	None
			C: 2–60 m	C: 30/30; 0	C: 20–62 y; 14/16			

Notes: C: Control; I: Intervention; m: months; mg: milligram; ml: milliliter; NS: not stated; po: administrated orally; qd: once daily; qn: once per night; tid: three times daily; w: weeks, y: years.

Table 6.2: Details of Chinese Herbal Medicine Formula: Chinese Herbal Medicine v. Antihistamines for Chronic Urticaria

First author, publication year	Key ingredients of Chinese herbal medicine
Bian XL 2006 (107)	*Dan long zhi yang jiao nang* (capsule): *he shou wu, bai shao, mu dan pi, di long, quan xie, bai xian pi*, and other (NS)
Chen H 2009 (109)	*Gui zhi tang* modification*: huang qi, gui zhi, bai shao, dang gui, sheng jiang, fang feng, mu dan pi, quan xie, da zao, zhi gan cao*
Chen XJ 2009 (101)	*Dang gui yin zi* (modified)*: dang gui, mu dan pi, bai shao, sheng di huang, bai ji li, huang qi, jing jie, fang feng, he shou wu, ji xue teng, yu zhu*
Huang N 2011 (110)	*Qu shi hua zhi jie du tang: fu ping, xu chang qing, wei ling xian, dan shen, ji xue teng, san qi, sheng di huang, tu fu ling, bai xian pi, chen pi, hua shi, gan cao*
Jin RJ 2006 (111)	*Wu wei zi tang: wu wei zi, fang feng, bai zhu, bai shao, huang qi, dang shen, gui zhi, zhi gan cao, sheng jiang, da zao*
Kong DY 2015 (105)	*Yu ping feng san modification: huang qi, jing jie, dang gui, bai zhu, fang feng, chen pi, fu ling, gui zhi, da fu pi, sang bai pi, gan cao*
Li AJ 2012 (112)	*Ma huang fu zi xi xin tang modification: ma huang, fu zi, xi xin, dang gui, he shou wu*
Li JY 2009 (103)	*Kang guo min ke li (granule): jing jie, fang feng, huang qin, huang bo, ku shen, bai xian pi, zi cao, di fu zi, chan tui, bai zhu, gan cao*
Li YB 2013 (102)	*Man xun yin: huang qi, bai xian pi, fang feng, wu wei zi*
Luo B 2006 (106)	*Xiao feng zhi yang ke li : huang qi, fang feng, jing jie, mu dan pi, bai ji li, fu ping, bai zhu, yin chai hu, zi cao, zhi gan cao* and other (NS)
Luo MY 2006 (113)	*Kang xun fang: sheng di huang, bai shao, dang gui, chuan xiong, jing jie, fang feng, he shou wu, bai ji li, gan cao*
Shi CR 2013 (99)	*Dang gui yin zi: dang gui, bai shao, chuan xiong, sheng di huang, bai ji li, fang feng, jing jie, he shou wu, huang qi, zhi gan cao*
Wang HL 2010 (104)	*Ma huang lian qiao chi xiao dou tang: ma huang, lian qiao, xing ren, sang bai pi, sheng jiang, chi xiao dou, zhi gan cao, da zao*
Wang L 2006 (115)	*Shu feng chu shi tang: jing jie, fang feng, yi yi ren, zhi ke, bai zhu, huang bo, sang ye, xu chang qing, sheng di huang, yin chen, gan cao*
Wo LY 2008 (116)	Self-designed *Ping min jian* modification*: long gu, mu li, he shou wu, chai hu, fang feng, jing jie, bai xian pi, jiang can, zhi ke, fu ping, wu mei, wu wei zi, mu dan pi, di gu pi, dang gui*
Wu H 2003 (114)	*Yu ping feng guo min jian: huang qi, bai zhu, fang feng, wu mei, wu wei zi, yin chai hu, zhi gan cao*
Xiao HL 2002 (117)	*Dang gui yin zi: dang gui, bai shao, chuan xiong, sheng di huang, bai ji li, fang feng, jing jie, he shou wu, huang qi, gan cao*

First author, publication year	Key ingredients of Chinese herbal medicine
Xue CL 2009 (100)	*Kang man min jian: chai hu, bai shao, fang feng, chan tui, di long, bai xian pi, tu fu ling, lian qiao, mu dan pi, huang qi, dang shen, bai zhu, dang gui, gan cao*
Yan X 2009 (118)	*Xiao xun fang: gui zhi, bai shao, di fu zi, sang bai pi, di gu pi, bai zhu, chi shao, gan cao*
Yang GH 2012 (120)	*Yang zhen tang: sheng di huang, dang gui, bai shao, sang ji sheng, chuan xiong, jing jie, fang feng, cang zhu, ku shen, zhi mu, niu bang zi, chan tui, gan cao*
Yang SR 2014 (121)	*Ma xing shi gan tang* modification*: ma huang, xing ren, shi gao, gan cao, shui niu jiao, xiao hong shen, bai xian pi, di fu zi, sheng di huang, mu dan pi, jiu li guang, bai hua she she cao*
Yu GH 2009 (119)	*Ping min jian* modification*: long gu, mu li, he shou wu, chai hu, fang feng, jing jie, bai xian pi, jiang can, zhi ke, fu ping, wu mei, wu wei zi, mu dan pi, di gu pi, dang gui*
Zhang BX 2013 (123)	*Ma huang lian qiao chi xiao dou tang* plus modified *Dang gui yin zi: ma huang, lian qiao, he shou wu, bai ji li, sang bai pi, sheng di huang, di gu pi, fu ling pi, chi xiao dou, fang feng, jing jie, huang qi, dang gui, chi shao, zhi zi, da qing ye, bai zhu, chan tui, bian dou yi, chuan xiong*
Zhang CJ 2011(108)	*Shu gan huo xue qu feng fang: chai hu, dang gui, chi shao, hong hua, bai zhu, chen pi, fang feng, jiang can, bai ji li, he huan pi*
Zhang EH 2007 (122)	*Guo min jian* modification*: jing jie, fang feng, yin chai hu, wu wei zi, wu mei, huang qi, bai zhu, huang qin, gan cao*
Zhu WR 2011 (124)	*Di shen qu feng he ji: sheng di huang, ku shen, cang er zi*, and other (NS)

Notes: NS: not stated

6.3.2 Outcome Measures

One study (99) used UAS to assess disease activity, reporting the change in UAS rather than the actual score. Another study (121) used a modified UAS as an outcome measure, which added the diameter of wheals into the UAS scoring system. All studies reported on ER, which was calculated using two approaches (see Chapter 5). Eleven studies reported ER 30 (100–104, 107, 109, 112, 114, 117, 120), while 15 reported SSRI 30 (99, 105, 106, 108, 110, 111, 113, 115, 116, 118, 119, 121–124). Relapse rate based on ER 30 was reported in three studies (103, 107, 117). None of the included studies assessed participants' HR-QoL.

6.3.3 Risk of Bias Assessment

While all studies claimed to be randomised, only five (99, 108, 112, 121, 124) described the methods for random sequence generation. Four of them used random number tables (108, 121, 124) or computer software (99), and these four studies (99, 108, 121, 124) were assessed as low risk for sequence generation (see Table 6.3). One study (112) was deemed high risk due to its use of consultation date to allocate participants. The remaining studies were assessed as posing an unclear risk due to lack of description for sequence generation. In terms of allocation concealment, one study (112) was considered high risk. The treatments in this study were predictable because visiting date was used to allocate participants. No detailed information of allocation concealment was provided for the remaining studies and all were judged as unclear risk. None of the studies used methods to blind participants and personnel to group allocation. Therefore, all studies were deemed high risk. All studies were judged as posing an unclear risk in terms of blinding of outcome assessors due to lack of information (see Table 6.3). One study (99) reported dropouts with reasons, and the numbers of dropouts was balanced between groups. There were no dropouts for the remaining studies. Therefore, the risk of bias for incomplete outcome data was assessed as low. All studies were considered

to pose an unclear risk in terms of selective outcome reporting due to lack of protocols or trial registration (see Table 6.3).

Table 6.3: Risk of Bias Assessment Results: Chinese Herbal Medicine v. Antihistamines for Chronic Urticaria

First author, publication year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
Bian XL 2006 (107)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Chen H 2009 (109)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Chen XJ 2009 (101)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Huang N 2011(110)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Jin RJ 2006 (111)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Kong DY 2015 (105)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Li AJ 2012 (112)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Li JY 2009 (103)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Li YB 2013 (102)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Luo B 2006 (106)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Luo MY 2006 (113)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Shi CR 2013 (99)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wang HL 2010 (104)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wang L 2006 (115)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wo LY 2008 (116)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wu H 2003 (114)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Xiao HL 2002 (117)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Xue CL 2009 (100)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yan X 2009 (118)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yang GH 2012 (120)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yang SR 2014 (121)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yu GH 2009 (119)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang BX 2013 (123)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang CJ 2011 (108)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang EH 2007 (122)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhu WR 2011 (124)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear

6.3.4 Effects of the Intervention

Urticaria Activity Score

Two studies reported on UAS (99, 121). One study reported UAS percentage score change from baseline (99), which differs from the prescribed use of the outcome measure. The difference between groups was not statistically different (MD: -0.13 [-0.84, 0.58]). The other (121) found no difference between CHM and levocetirizine (MD: -0.77 [-1.64, 0.10]) in terms of modified UAS score at the end of treatment.

Effective Rate 30

The pooled data of 11 studies (100–104, 107, 109, 112, 114, 117, 120) showed that CHM was superior to antihistamines in improving symptoms by 30% or more (RR: 1.21 [1.15, 1.29], I^2=0%) (see Figure 6.2). One CHM formula (*Dang gui yin zi*) was used in two studies (101, 117) and analysis found no significant difference between groups (RR: 1.18 [0.93, 1.50], I^2 = 49%) (see Figure 6.2).

Symptom Severity Reduction Index 30

Meta-analysis of 15 studies (99, 105, 106, 108, 110, 111, 113, 115, 116, 118, 119, 121–124) found significant improvement in favour of CHM when compared with antihistamines (RR: 1.18 [1.07, 1.29], I^2 = 72%) (see Figure 6.3). Statistical heterogeneity was detected, which was explored by sensitivity and subgroup analyses. When only studies assessed as having a low risk of bias for sequence generation were included (99, 108, 121, 124), statistical heterogeneity reduced (I^2 = 61%), although the treatment effect was no longer significant (RR: 1.12 [0.91, 1.39]).

Subgroup group analysis according to comparator types found significant difference when comparing CHM to levocetirizine (RR: 1.32 [1.20, 1.45], I^2 = 0%) (105, 108, 110, 121, 123) and no difference for loratadine (RR: 1.07 [1.00, 1.14]; I^2 = 0%) (106, 111, 115, 118, 124), with low statistical heterogeneity (see Figure 6.3). No benefit was observed for CHM compared with cetirizine (RR: 1.36 [0.94, 1.97], I^2 = 80%) (99, 116, 119, 122), but statistical heterogeneity was considerable (see Figure 2.2). One investigator-designed CHM formula, *Ping min jian* (modified), was used in two studies (116, 119), with no difference found (RR: 1.39 [0.94, 2.05], I^2 = 86%). Considerable heterogeneity was detected, which could not be explored due to the small number of studies.

Relapse Rate

The pooled data of three studies suggested that CHM reduced the risk of relapse compared with antihistamines (RR: 0.31 [0.16, 0.63], I^2 = 22%) (103, 107, 117).

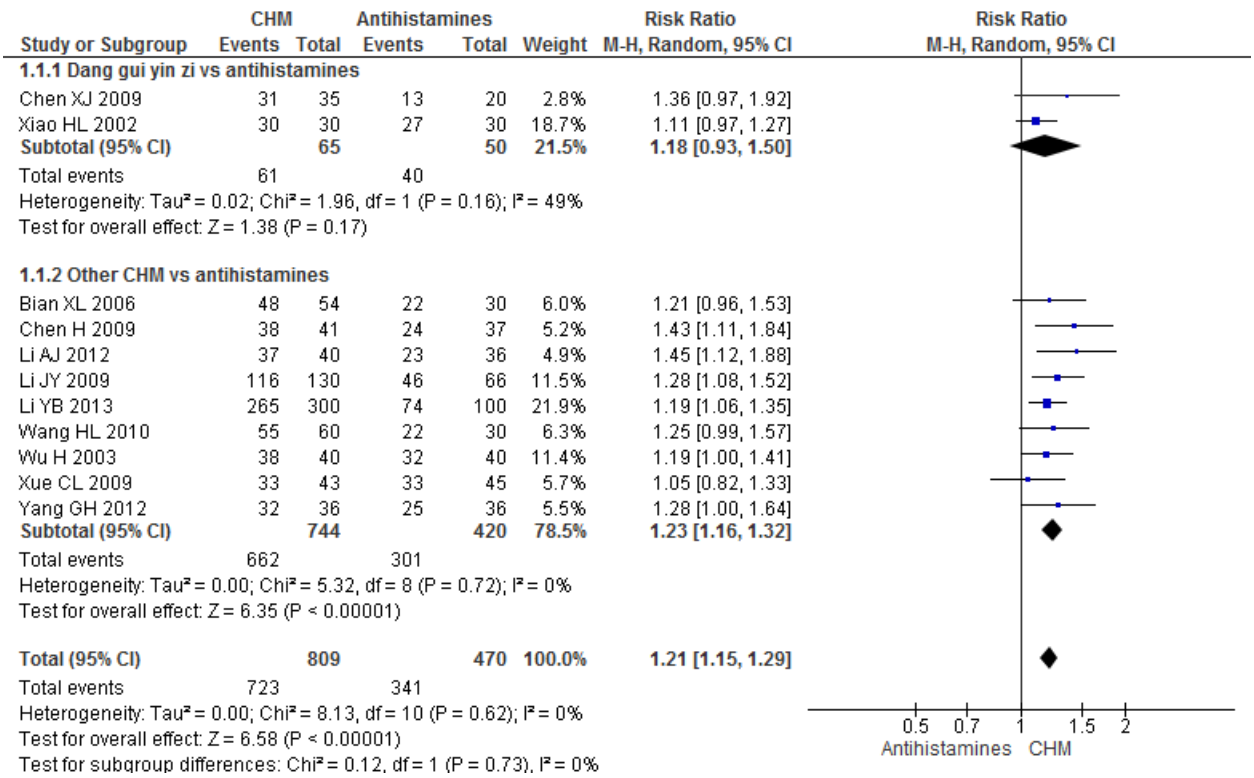

Figure 6.2: Effect Size Analysis Results of Chinese Herbal Medicine v. Second-Generation Antihistamines for Chronic Urticaria: ER 30

Notes: CHM: Chinese herbal medicine; ER 30: effective rate based on Chinese Medicine guideline

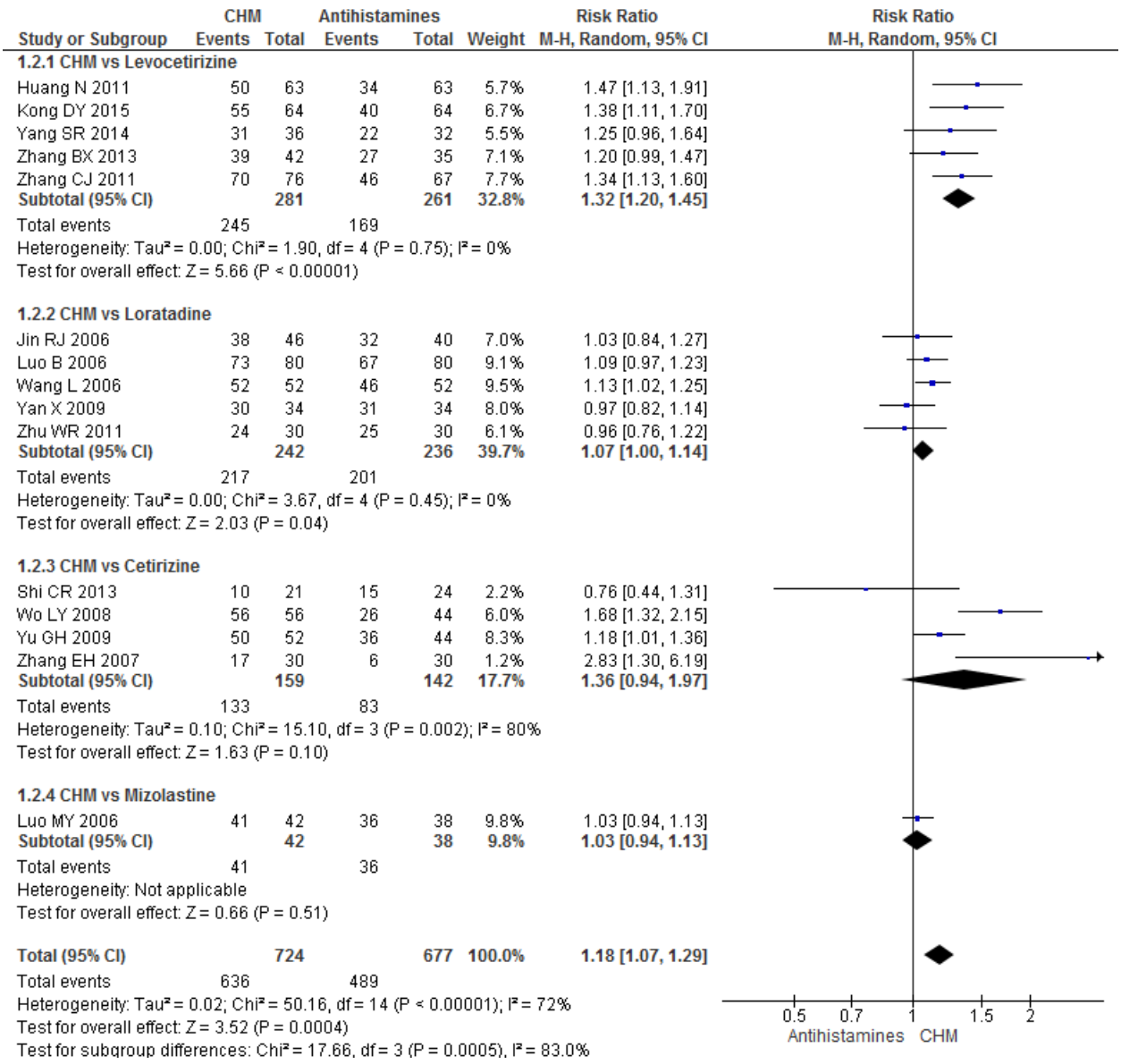

Figure 6.3: Effect Size Analysis Results of Chinese Herbal Medicine v. Second-Generation Antihistamines for Chronic Urticaria: SSRI 30

Notes: CHM: Chinese herbal medicine; SSRI 30: effective rate based on Symptom Severity Reduction Index

6.3.5 Adverse Events

Thirteen studies (99, 105, 106, 108, 110, 111, 113, 115, 118, 120, 122–124) reported on adverse events (AEs), with two reporting no AEs (110, 124). In the remaining studies, 29 AEs were

reported in the CHM groups and 77 AEs in antihistamines groups. The AEs that occurred in the CHM groups included diarrhoea (21 cases), somnolence (five cases), nausea (two cases) and gastrointestinal discomfort (one case). In the antihistamines groups, the most commonly observed AE was somnolence (22 cases). Other AEs involved weakness (13 cases), hyperphagia (12 cases), dizziness and weakness (nine cases), thirst (nine cases), dizziness (six cases), dizziness and headache (two cases), nausea (two cases), poor appetite (one case) and loose stool (one case).

6.3.6 Publication Bias

The funnel plot for ER 30 (11 studies) was symmetrical (see Figure 6.4), which suggests a low risk of publication bias. Potential bias should be noted for SSRI 30 (15 studies) and relapse rate based on SSRI 90 (11 studies). This is illustrated in the funnel plot, with a slight asymmetrical distribution of the studies (see Figure 6.5).

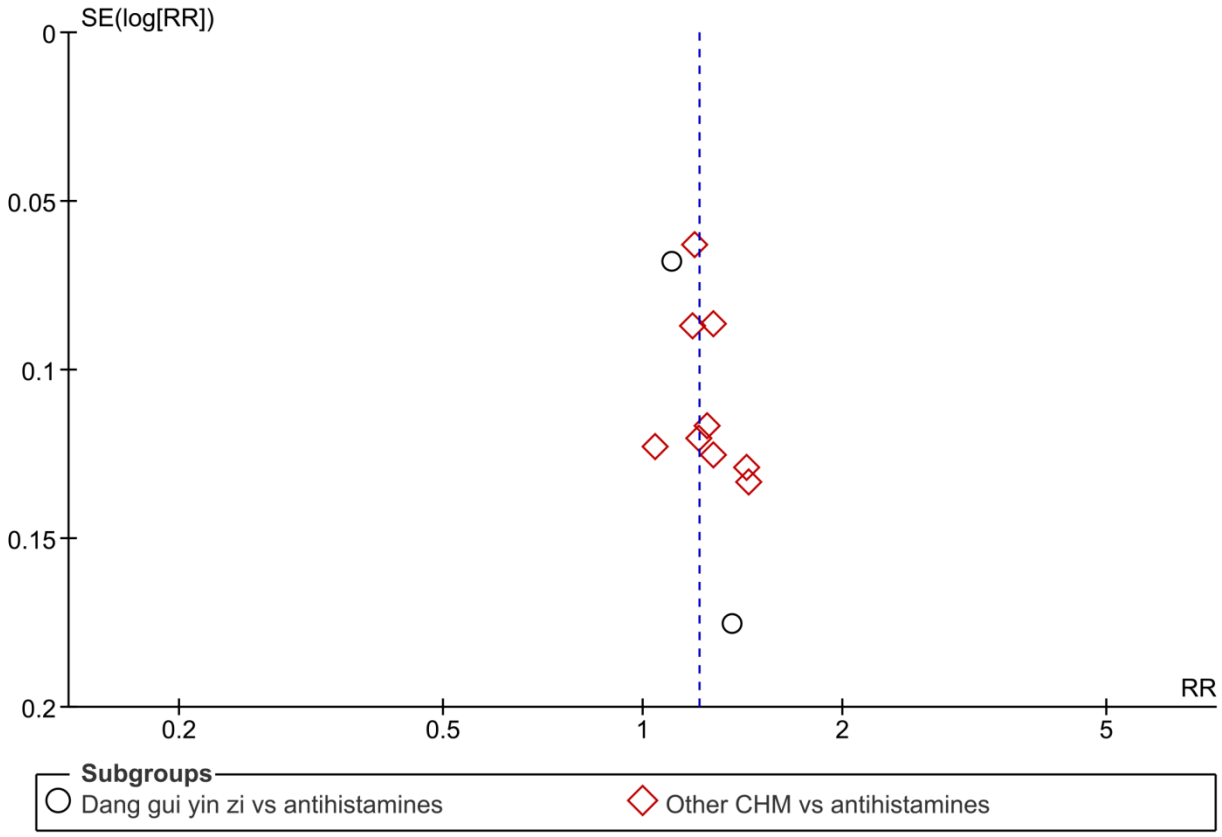

Figure 6.4: Funnel Plot of Chinese Herbal Medicine v. Antihistamines for Chronic Urticaria: ER 30

Notes: CHM: Chinese herbal medicine; ER 30: effective rate based on Chinese medicine guideline

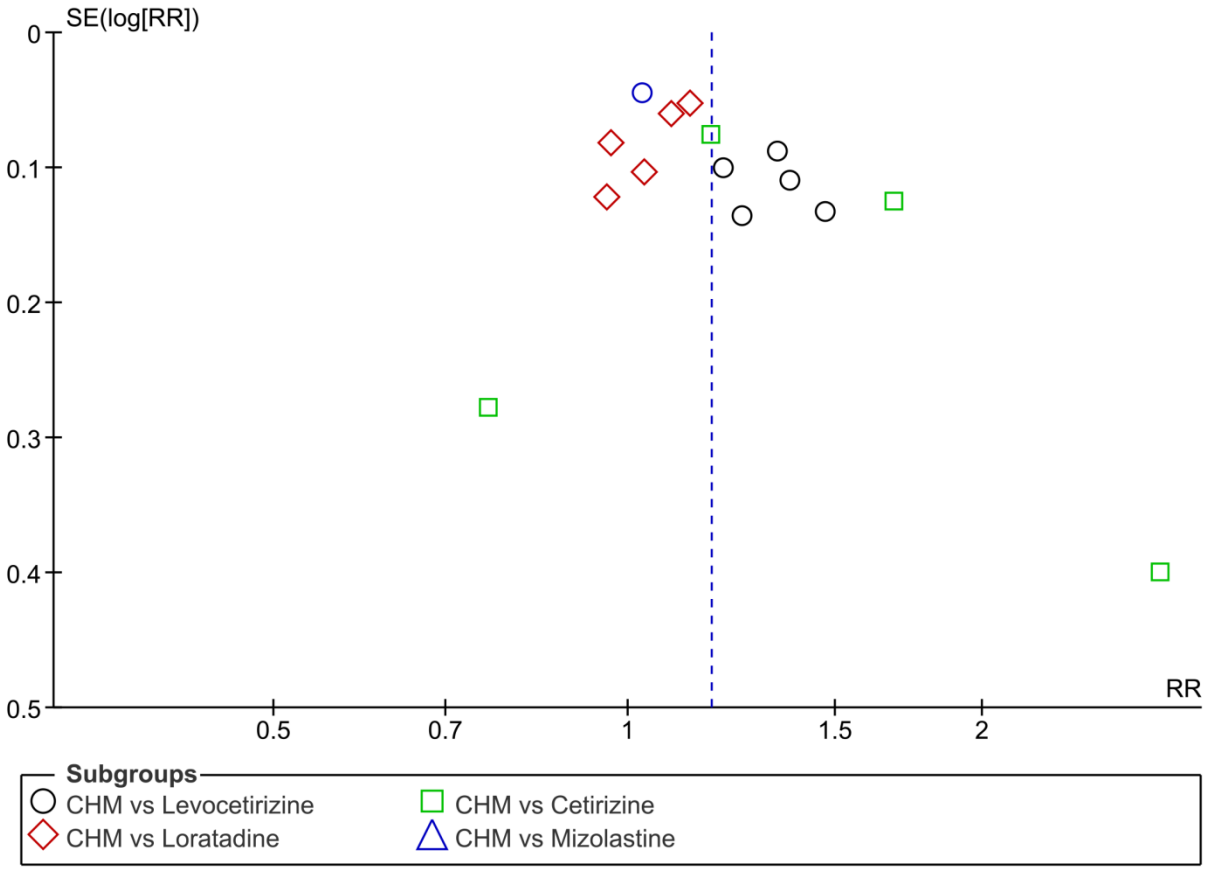

Figure 6.5: Funnel Plot of SSRI 30 (Chinese Herbal Medicine v. Antihistamines for Chronic Urticaria)

Notes: CHM: Chinese herbal medicine; SSRI 30: effective rate based on Symptom Severity Reduction Index

6.4 Discussion

Meta-analysis indicated that CHM increased the chance of achieving improvement in wheals and pruritus compared with second-generation antihistamines. Studies reporting on ER 30 were homogenous, while those reporting on SSRI 30 were heterogeneous. The heterogeneity was reduced somewhat through sensitivity and subgroup analyses. The source of heterogeneity may be attributed to selection bias and antihistamine use. When sensitivity analysis was conducted using studies with low risk of bias for sequence generation, heterogeneity reduced. Further, heterogeneity decreased dramatically when subgroup analysis was performed by antihistamine type. It was noted that the heterogeneity was 80% for the subgroup comparing CHM with cetirizine, despite consistency in dosage and frequency. The reason for heterogeneity was still unclear.

In addition, the effectiveness threshold of SSRI was not consistent across studies. Some studies reported a 20% improvement in symptoms, some reported a 25% improvement, while others cited a 30% improvement. To ensure uniformity in outcomes, only data that reported an improvement rate of 30% or more were pooled for analysis. This meant that for studies reporting a 20% change, only data for the next tier (for example, 60% improvement) were included. This may have contributed to statistical heterogeneity in the meta-analysis. However, when additional subgroup analysis was performed according to tier, heterogeneity was not reduced (data not presented).

As data for studies reporting on the same outcome were pooled regardless of CHM formula used, it was reassuring to observe that statistical heterogeneity was low for many analyses. When individual formulae were examined in meta-analysis, *Dang gui yin zi* 当归饮子 and *Ping min*

jian 平敏煎 modification failed to demonstrate benefit, with considerable statistical heterogeneity. This may be due to the small sample size of included studies, although a lack of benefit for these formulae cannot be ruled out.

Only one study used UAS (99), and no difference was found between groups in terms of score change. Another study used modified UAS (121) to evaluate the effect but did not discover a significant difference. There is a clear need for well-designed RCTs that report on validated outcome measures such as the UAS.

The number of AEs in participants who received CHM was lower than in those who received antihistamines. The high number of cases of somnolence with antihistamines was surprising, as second-generation antihistamines are not considered to have sedating effects. Most AEs in CHM groups were gastrointestinal symptoms, which has been observed in other health conditions (125). Based on the studies that reported this outcome, CHM was well tolerated by patients with chronic urticaria.

The most frequently reported herbs in CHM formulae included in the studies appear to have anti-inflammatory, anti-allergenic and antipruritic actions. Inhibition of inflammatory mediator nitric oxide (NO) has been found in murine macrophage RAW 264.7 cells with *fang feng* 防风 (*Saposhnikovia divaricata* [Turcz.] Schischk) (126), *gan cao* 甘草 (*Glycyrrhiza spp*) (127) and *dang gui* 当归 (*Angelica sinensis* [Oliv.] Diels) (128). Pro-inflammatory cytokines tumour necrosis factor (TNF)-α and interleukin-6 (IL-6) have also been reduced by *fang feng* 防风 (126), *gan cao* 甘草 (127), *dang gui* 当归 (128), *jing jie* 荆芥 (*Schizonepeta tenuifolia* Briq.) (129), and *huang qi* 黄芪 (*Astragalus membranaceus* [Fisch] Bge.) (130). *Gan cao* 甘草, *huang qi* 黄

芪 and *jing jie* 荆芥 inhibited histamine levels and histamine release in RBL-2H3 cell line and rat peritoneal mast cells (131), in rats with haemorrhagic shock (132) and in a rat model (133). Scratch behaviour was inhibited with *gan cao* 甘草 (131) and *jing jie* 荆芥 (134). The anti-inflammatory, anti-allergenic and antipruritic actions of these herbs are likely to contribute to the clinical effect observed in this review.

6.4.1 Limitations and Implications for Research and Clinical Practice

The methodological issues of included studies must be carefully considered for these findings. Only four studies described detailed and appropriate methods of sequence generation, despite all studies claiming to be RCTs. Potential selection bias may exist since the generation of a randomised sequence might be inadequate for most studies. Outcome assessment might be less reliable due to insufficient information of blinding (89). Moreover, most studies had small sample sizes. Randomised, double-blinded, placebo-controlled trials with large sample sizes are necessary to verify the treatment effect of CHM for chronic urticaria.

UAS was used in two studies, but was modified or calculated differently from prescribed use. The outcomes (ER 30 and SSRI 30) were commonly used in the included studies. Although these two outcomes evaluated the disease activity of the two main urticaria symptoms (wheals and pruritus) and reflected the clinical focus, they are not recognised internationally and have not been validated. This limits the findings' comparability with other international studies. Validated outcomes should be introduced into future clinical trials to evaluate the efficacy of CHM for chronic urticaria.

None of the included studies assessed participants' HR-QoL. This is an important outcome for which validated measures are available and should be included in future trials. The challenge of chronic urticaria is to achieve effective control to prevent recurrence of symptoms. Relapse rates were reported by several studies. However, the definition of relapse rate varied. Greater consistency is needed to examine the potential long-term benefits of CHM for chronic urticaria.

In clinical practice, CHM formula is prescribed based on CM syndrome type, ensuring individualised treatment. Few studies included in this review reported information related to syndrome types and meta-analysis could not be performed according to syndrome. The findings from this review may not reflect the clinical efficacy of CHM when used according to CM principles and may introduce potential clinical heterogeneity. Further, clinical trials that consider syndrome type in study design and analysis may provide results that are more reflective of clinical practice.

6.5 Conclusion

Considering the limitations mentioned above, the findings from this review suggest that CHM can improve symptoms of chronic urticaria (based on ER 30) when compared with second-generation antihistamines. However, the methodological flaws of included studies and lack of validated outcome measures limit the certainty of these findings. CHM appears to be well tolerated by patients with chronic urticaria, as illustrated by the low number of AEs reported in the included studies. Future research following rigorous study design with validated outcomes is needed to provide robust evidence.

Chapter 7. Systematic Review 2:

Chinese Herbal Medicine as Add-on Therapy for Chronic Urticaria

7.1 Introduction

For people with chronic urticaria, CHM is a treatment option commonly used in clinical practice in China. Chapter 6 evaluated the evidence of CHM alone for chronic urticaria when compared with second-generation antihistamines. CHM is also commonly used in combination with conventional treatments. To date, no SRs were identified that evaluated the additional benefits of adding CHM to conventional therapy. The objective of this SR is to evaluate the efficacy and safety of CHM as an add-on therapy to second-generation antihistamines for chronic urticaria.

7.2 Method

The methods for SR of CHM for chronic urticaria were described in Chapter 5. This review has been registered in PROSPERO (CRD42015027765).

7.3 Results

Extensive database searches retrieved 7,631 potentially relevant citations. After removing duplicates, 5,666 records were screened and full texts of 1,925 were identified (see Figure 7.1). Seventy-four RCTs met the inclusion criteria and were included in this review. Four were excluded from meta-analysis due to a lack of usable data (135–138). All studies were conducted in China. They were published between 2004 and 2015 in Chinese except for two published in English (138, 139). Two-arm parallel design was applied for most studies and eight studies include three or more arms (99, 100, 135, 140–144). Blinding was only described in one study

(138), with participants, researchers and outcome assessors being blinded to group allocation (see Table 7.1).

In total, 7,497 patients with chronic urticaria from outpatient or inpatient departments of hospitals were recruited in the included studies. The sample size of included studies ranged from 37 (145) to 360 (140). Participants' ages ranged from one (146) to 78 years (147) (see Table 7.1). Treatment duration ranged from seven days (148) to 12 weeks (142, 149–151). The most common treatment duration was four weeks. Follow-up assessments were mentioned in 51 studies, ranging from two weeks to 52 weeks after the initial treatment (see Table 7.1). Two studies reported the number of participants suffering relapse after achieving a clinical cure for the outcome ER 30 (152, 153).

7.3.1 Intervention and Co-intervention/Comparator

CHM was administered orally in all studies (see Table 7.1). CHM was used as decoction in 33 studies, as capsules in 21 studies, as granules in 13 studies, as tablets in five studies and as pills in two studies. A variety of CHM formulae and compound products were used in the 74 included studies (see Table 7.2). The most frequently used CHM formulae or compound products were total glycosides of paeony (from *bai shao* 白芍) 白芍总苷 (10 studies), *Yu ping feng san* 玉屏风散 (nine studies), CG (from *gan cao* 甘草) 复方甘草酸苷 (six studies) and tripterygium glycosides (from *lei gong teng* 雷公藤) 雷公藤多苷 (four studies). The most frequently used herbs in the included studies were *fang feng* 防风 (*Saposhnikovia divaricata* [Turcz.] Schischk.) (35 studies), *huang qi* 黄芪 (*Astragalus membranaceus* [Fisch] Bge.) (27 studies), *dang gui* 当归 (*Angelica sinensis* [Oliv.] Diels.) (26 studies), *gan cao* 甘草 (*Glycyrrhiza spp*) (25 studies), *jing*

jie 荆芥 (*Schizonepeta tenuifolia* Briq.) (22 studies) and *bai zhu* 白术 (*Atractylodes macrocephala* Koidz.) (20 studies). Three herbs used together comprise *Yu ping feng san* 玉屏风散: *fang feng* 防风, *huang qi* 黄芪 and *bai zhu* 白术. Most studies adopted a two-arm design and used second-generation H1-antihistamines as co-intervention in the intervention group and the comparator in the control group. The most commonly used agents were cetirizine, levocetirizine or loratadine. Oral administration of antihistamines was in dosages of five mg or 10 mg daily (see Table 7.1). The antihistamine agents used as co-intervention were the same as the comparator, as were the dosages. A few studies employed two or more control groups, including various antihistamines agents or CHM (99, 100, 140–144). The usage of CHM in the control was also same as in the intervention group, but these data were not analysed in this SR.

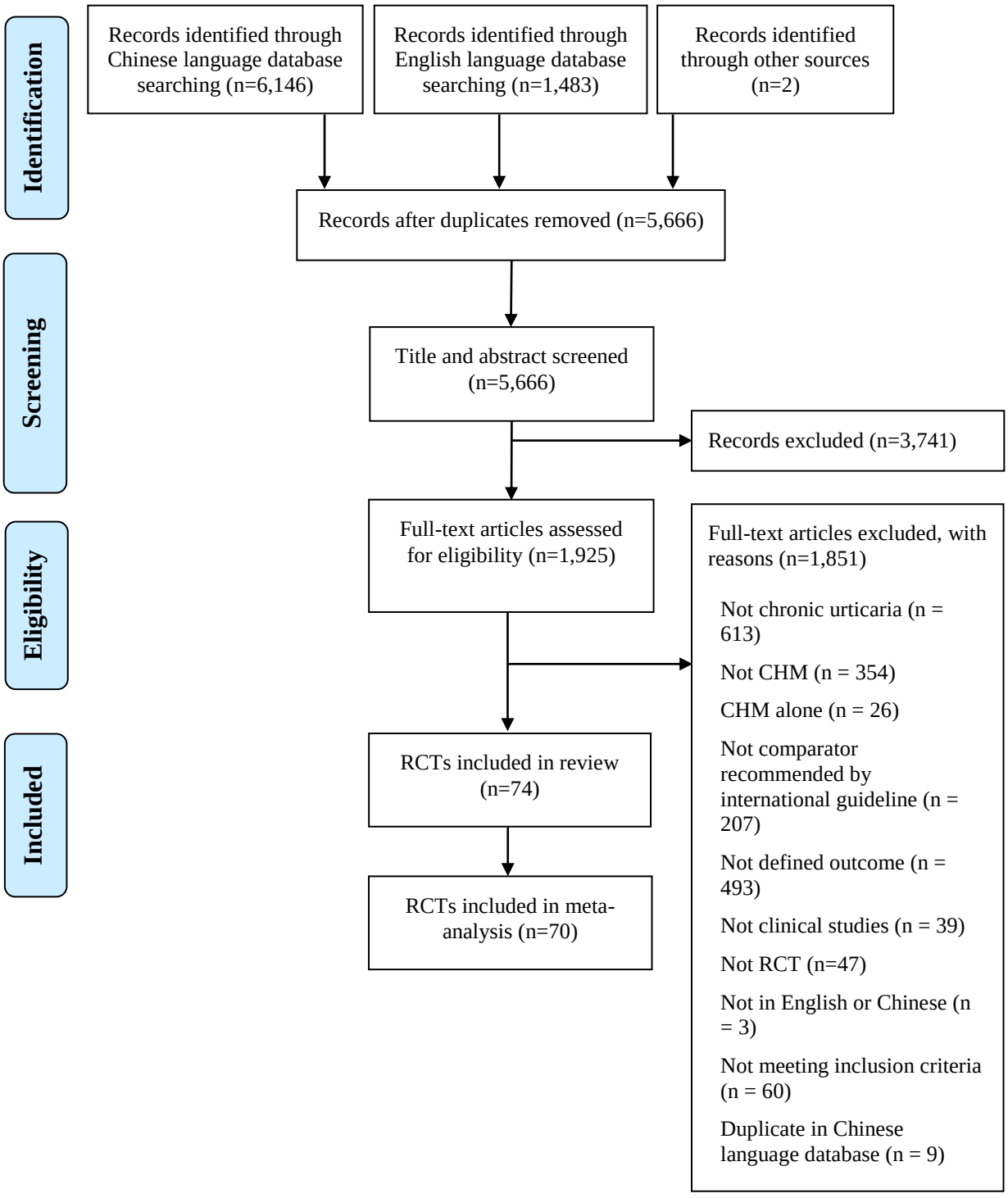

Figure 7.1: PRISMA Flow Chart of Study Selection Process: Chinese Herbal Medicine as Add-on Therapy v. Second-Generation Antihistamines for Chronic Urticaria

Notes: CHM: Chinese herbal medicine; RCT: randomised controlled trial

Table 7.1: Characteristics of Included Randomised Controlled Trials: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Bai WJ 2011 (177)	NS; 2	21 d; 4 w	Total: 4.5 y	I: 34/34; 0 C: 34/34; 0	Total: 31.4 y; 32/36	*Xiao feng san* (decoction): bid, po	Loratadine: 10 mg qd, po
Bao LX 2008 (176)	NS; 2	4 w; NS	Total: 19.2 m	I: 87/87; 0 C: 80/80; 0	Total: 36. 3y; 77/90	*Tripterygium glycosides* (tablets): 10 mg tid, po	Desloratadine: five mg qd, po
Chen CS 2015 (194)	NS; 2	8 w; 4 w	Total: NS	I: 42/42; 0 C: 41/41; 0	I: 31 (1) y; 20/22 C: 30 (2) y; 20/21	*Yu ping feng ke li* (granule): five gm tid, po	Azelastine 2 mg bid, po
Chen JY 2014 (181)	NS; 2	4 w; NS	I: 1 y C: 1.5 y	I: 47/47; 0 C: 46/46; 0	I: 26 y; 23/24 C: 28 y; 22/24	*Xiao yin ke li* (granule): 3.5 g tid, po	Ebastine: 10 mg qd, po
Chen XB 2011 (145)	NS; 2	21 d; NS	I: 8 m–3 y C: 6 m–2 y	I: 22/22; 0 C: 15/15; 0	I: 25–45; 9/13 C: 25–45; 8/7	Unnamed formula (decoction): bid, po; qd, topical use (bath)	Loratadine: 10 mg qd, po
Cheng Y 2010 (175)	NS; 2	4 w; 1 m	I: 13.3 m C: 13.1 m	I: 30/30; 0 C: 30/30; 0	I: 8.5 y; NS C: 7.5 y; NS	*Ba zhen san plus si wu xiao feng san* (decoction): usage not specified	Loratadine: 2–6 years old: syrup, >6 years old: tablets; <2 years old:2.5 mg daily; 2–8 years old: 5 mg daily; >8 years old: 10 mg daily
Deng D 2012 (174)	NS; 2	4 w; 2 m	Total: 2 m-10 y	I: 42/42; 0 C: 41/41; 0	Total: 18–65 y; 38/45	*Pi min xiao jiao nang* (capsule): 4 capsules tid, po	Fexofenadine: 60 mg bid, po

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Ding QY 2007 (173)	NS; 2	28 d; NS	Total: 1.7 y	I: 50/50; 0 C: 50/50; 0	Total: 18–70 y; 56/44	*Run zao zhi yang jiao nang* (capsule): four capsule, tid, po	Levocetirizine: 10 mg qd, po
Feng S 2015 (195)	NS; 2	8 w; 6 m	I: 15.22 (21.51) m C: 1.39 (1.45) y	I: 54/52; 2 C: 54/52; 2	I: 39.59 (14.45) y; 25/29 C: 38.80 (14.41) y; 23/31	*Qu feng qing re wei ling tang* (decoction): bid, po	Loratadine: 10 mg qd, po
Fu YH 2011 (141)*★	NS; 4	8 w; 3 m	Total: NS	I: 30/30; 0 C1: 30/30; 1 C2: 30/30; 0 C3: 30/30; 0	Total: 12–65 y; NS	Fortifying the Spleen and nourishing Blood or dispelling wind (modified decoction): bid, po; cetirizine: used as control group 1	C1: Cetirizine: 10 mg qd, po C2: Fortifying the Spleen and nourishing Blood (modified decoction): bid, po C3: Dispelling wind: bid, po
Guo XY 2014 (182)	NS; 2	4 w; NS	Total: NS	I: 42/42; 0 C: 25/25; 0	Total: NS; NS	Compound glycyrrhizin (tablets): 75 mg, tid, po	Mizolastine: 10 mg qd, po
Huang SY 2012 (206)	NS; 2	7 d; NS	I: 3 m–2.5 y C: 3 m–3 y	I: 35/35; 0 C: 35/35; 0	I: 21–65 y; 18/17 C: 20–63 y; 16/19	*Guo min jian* (decoction): 200 ml tid, po	Cetirizine: 10 mg qd, po
Jiang YP 2009 (172)	NS; 2	4 w; 4 w	Total: 2 m–6 y	I: 76/76; 0 C: 64/64; 0	Total: 14-60 y; 78/62	*Qi feng ke li* (granules): 10 g tid, po	Cetirizine: 10 mg qd, po

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Jiang YP 2011 (151)	NS; 2	12 w; 3 m	I: 25.89 (44.55) m	I: 43/43; 0	I: 25.44 (11.25) y; 20/23	Compound glycyrrhizin (capsule): 50 mg tid, po	Setastine: one mg bid, po
			C: 27.71 (45.26) m	C: 37/37; 0	C: 34.53 (13.26) y; 20/17		
Jie SH 2014 (135)★	NS; 3	4 w/12 w; 52 w	I1: 1.3 (0.5) y	I1: 50/50; 0	I1: 31.0 (8.9) y; 26/24	I1: Total glycosides of paeony (capsule): 600 mg bid, po for 12 weeks; desloratadine: used as per control group I2: Total glycosides of paeony (capsule): 600 mg bid, po for four weeks; desloratadine: used as per control groups	Desloratadine: 8.8 mg qd, po for four weeks
			I2: 1.4(0.4) y	I2: 50/50; 0	I2: 29.0 (7.8) y; 25/25		
			C: 1.5 (0.5) y	C: 50/50; 0	C: 35.0 (8.7) y; 24/26		
Leng J 2014 (136)	NS; 2	4 w; 4 w	Total: 1.5 y	I: 50/50; 0	Total: 36y; 54/46	*Run zao zhi yang jiao nang* (capsule): four capsules tid, po	Ebastine: 10 mg qd, po
				C: 50/50; 0			
Li CH 2014 (183)	NS; 2	4 w; 4 w	I: 1.15 (0.76) y	I: 61/61; 0	I: 39.36 (16.89) y; 28/23	*Yu ping feng ke li* (granule): five g tid, po	Cetirizine: 10 mg qd, po
			C: 1.08 (0.48) y	C: 61/61; 0	C: 36.10 (15.27) y; 25/26		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Li ZL 2013 (171)	NS; 2	1 m; 1 m	I: 13.5 (10.6) m	I: 54/54; 0	I: 32.6 (16.5) y; 28/26	*Qing re xiao feng san* (decoction): 200 ml bid, po	Desloratadine: five mg qd, po
			C: 14.3 (11.2) m	C: 46/46; 0	C: 34.3 (15.7) y; 25/21		
Liao C 2014 (184)	NS; 2	4 w; 3 m	Total: 0.57 (0.30) y	I: 58/58; 0 C: 58/58; 0	Total: 35.25 (6.82) y; 50/66	*Yu ping feng ke li* (granule): 10 g tid, po	Cetirizine: 10 mg bid, po
Lin YP 2012 (149)	NS; 2	12 w; NS	I: 23 m	I: 26/26; 0	I: 32.76 y; 9/17	Total glycosides of paeony (capsule): 600 mg tid, po	Cetirizine: 10 mg qd, po
			C: 27 m	C: 21/21; 0	C: 27.13 y; 7/14		
Lin ZF 2014 (142)★	NS; 3	12 w; NS	I: 8.9 w	I: 65/63; 2	I 29 y; 22/43	*Yu ping feng ke li* (granule): five g tid, po; levocetirizine: used as per control group 1	C1: Levocetirizine: five mg qd, po C2: *Yu ping feng ke li* (granule): 5 g tid, po; levocetirizine: 5 mg qd, po; increasing one day interval to use every other week
			C1: 9.5 w	C1: 65/60; 5	C1: 27.8 y; 25/40		
			C2: 9.1 w	C2: 65/65; 0	C2: 30 y; 28/37		
Liu Y 2014 (185)	NS; 2	4 w; NS	I: 3.4 (1.8) y	I: 53/53; 0	I: 31.8 (10.6) y; 27/26	*Fu fang di fu zi tang* (decoction): bid, po	Mizolastine: 10 mg qd, po
			C: 3.6 (1.9) y	C: 53/53; 0	C: 31.9 (10.9) y; 28/25		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Long JW 2010 (139)	NS; 2	4 w; 1 m	I: 8.9 (7.8) m	I: 65/63; 2	I: 36.5 (13.3); 37/28	Total glucosides of peony (capsule): two capsules tid, po	Cetirizine: 10 mg qd, po
			C: 9.6 (9.2) m	C: 55/48; 7	C: 35.3 (12.6); 32/22		
Lu JM 2007 (180)	NS; 2	4 w; NS	I: 8 w–7 y	I: 48/48; 0	I: 13–75 y; 20/28	*Qu feng xiao zhen tang* (decoction): bid, po	Cetirizine: 10 mg qd, po
			C: 8 m–6 y	C: 48/48; 0	C: 12-69y; 21/27		
Lu XY 2010 (205)	NS; 2	4 w; 1 m	Total: 3.5 (2.7) y	I: 74/74; 0	Total: 30.48 (7.61) y; 63/85	*Yu ping feng san* (modified decoction): 200ml bid, po	Levocetirizine: 5 mg qd, po
				C: 74/74; 0			
Ma LB 2012 (170)	NS; 2	4 w; 2 w	I: 2 m–6 y	I: 43/43; 0	I: 42 y; 19/24	*Qi feng ke li* (granules): 10 g tid, po	Mizolastine: dosage not specified, qd, po
			C: 2.5 m–5 y	C: 41/41; 0	C: 42 y; 18/23		
Ma WH 2010 (169)	NS; 2	4 w; NS	I: 6 w–3 y	I: 35/35; 0	I: 15–62 y; 19/16	*Wu she zhi yang wan* (pills): 2.5 g tid, po	Mizolastine: 10 mg qd, po
			C: 6 m–3.2 y	C: 35/35; 0	C: 14-61 y; 20/15		
Ma XM 2013 (178)	NS; 2	4 w; 6 m	I: 2.95 y	I: 62/62; 0	I: 32.5 y; 33/29	*Yu ping feng san* (decoction): bid, po	Mizolastine: 10 mg qd, po
			C: 3 y	C: 58/58; 0	C: 31.8 y; 32/26		
Mei T 2014 (186)	NS; 2	6 w; 6 m	Total: 6 m–1 y	I: 30/30; 0	Total: 20–58 y; 32/28	*Yu ping feng jiao nang* (capsule): two capsules bid, po	Mizolastine: 10 mg qd, po
				C: 30/30; 0			
Mou Y 2011 (168)	NS; 2	NS; 4 w	I: 3.3 (1.76) y	I: 30/30; 0	I: 30.6 (10.5) y; 13/17	Total glycosides of paeony (capsules): 0.6 g tid, po	Mizolastine: 10 mg qd, po
			C: 3.1 (1.56) y	C: 30/30; 0	C: 31.8 (10.2) y; 10/20		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Mi L 2008 (204)	NS; 2	4 w; 6 m	I: 2.92 (0.81) y	I: 35/35; 0	I: 35.16 (1.21) y; 19/16	*Jia wei yang he tang* (decociton): bid, po	Cetirizine: 10 mg qd, po
			C: 2.74 (0.69) y	C: 35/35; 0	C: 32.11 (2.23) y; 18/17		
Qian M 2011 (140)★	NS; 6	4 w; 4 w	Total: 6.62 (3.66) m	I1: 62/62, 0; I2: 61/61, 0; I3: 57/61, 0 C1: 61/60, 0; C2: 60/57, 0; C3: 59/59, 0	Total: 35.6 (9.7) y; 192/168	I1: Tripterygium glycosides (tablets): 60 mg qd, po; loratadine: used as per control group 1	C1: loratadine: 10 mg qd, po
						I2: Tripterygium glycosides (tablets): 60 mg qd, po; mizolastine: used as per control group 2	C2: mizolastine: 10 mg qd, po
						I3: Tripterygium glycosides(tablets): 60 mg qd, po; cetirizine: used as per control group 3	C3: cetirizine: 10 mg qd, po

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Shi CR 2013 (99)★	NS; 3	28 d; 3 m, 6 m	I: 1.80 (0.45) y	I: 25/22; 3	I: 35.37 (13.54) y; 11/14	*Dang gui yin zi* (decoction): bid, po; cetirizine: used as control group 1	C1: Cetirizine: 10 mg qd, po C2: *Dang gui yin zi* (decoction): bid, po
			C1: 1.50 (0.62) y	C1: 25/24; 1	C1: 36.63 (13.98) y; 12/13		
			C2: 1.60 (0.56) y	C2: 25/21; 4	C2: 34.14 (12.64) y; 13/12		
Song SH 2015 (144)★	NS; 3	30 d; 6 m	I: 3.4 (1.5) y	I: 52/52; 0	I: 36.5 (13.9) y; 27/25	*Xiao yin fang* (decoction): bid, po; ebastine: used as per control group 1	C1: Ebastine: 10 mg qd, po C2: *Xiao yin fang* (decoction): bid, po
			C1: 3.6 (1.2) y	C1: 43/42; 1	C1: 34.6 (12.7) y; 23/20		
			C2: 3.5 (1.4) y	C2: 38/38; 0	C2: 35.8 (13.2) y; 20/18		
Sun H 2015 (196)	NS; 2	8 w; 4 w	I: 1.45 (1.01) y	I: 118/118; 0	I: 35.80 (9.67) y; 56/62	*Qu feng kang min jian* (decoction): bid, po	Ebastine: 10 mg qd, po
			C: 1.39 (1.45) y	C: 116/116; 0	C: 36.53 (10.25) y; 54/62		
Sun RF 2007 (203)	NS; 2	28 d; 2 m	I: 10.2 m	I: 36/36; 0	I: 34 y; 14/22	Unnamed formula (decoction): bid, po	Levocetirizine: 10 mg qd, po (week 1–2); 10 mg qod, po (week 3); 10mg every two days, po (week 4);
			C: 9.9 m	C: 32/32; 0	C: 33.6 y; 12/20		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Sun RH 2014 (187)	NS; 2	4 w; NS	I: 27 m C: 22 m	I: 42/42; 0 C: 39/39; 0	I: 29.7 y; 28/14 C: 28.1 y; 21/18	*Run zao zhi yang jiao nang* (capsule): four capsules tid, po	Desloratadine: 8.8 mg qd, po
Sun RL 2014 (188)	NS; 2	8 w; NS	I: 19.6 m C: 17.8 m	I: 88/88; 0 C: 80/80; 0	I: 38.5 y; 36/52 C: 39.8 y; 31/49	Total glycosides of paeony (capsule): 600 mg tid, po	Fexofenadine: 60 mg bid, po
Tian AP 2011 (202)	NS; 2	14 d; 6 m	I: 3.6 y C: 3.5 y	I: 45/45; 0 C: 45/45; 0	I: 36 y; 24/21 C: 36.5 y; 27/18	*Fang ci yin hua fang* (decoction): bid, po	Levocetirizine: five mg qd, po
Tian J 2015 (197)	NS; 2	4 w; 4 w	I: 13.5 m C: 15 m	I: 53/53; 0 C: 53/53; 0	I: 36.5 y; 26/27 C: 18–63 y; 25/28	Compound glycyrrhizin (capsule): 50 mg tid, po	Mizolastine: 10 mg qd, po
Wang N 2011 (167)	NS; 2	4 w; 1 m	I: 13.5 m C: 14.4 m	I: 23/23; 0 C: 17/17; 0	I: 9.2 y; 11/12 C: 9.8 y; 10/7	*Si wu xiao feng san* (decoction): 50 ml bid, po	Setastine: one mg qd, po (age: <8 y); 1mg bid, po (age: 8–14 y)
Wang NL 2010 (201)	NS; 2	4 w; NS	I: 5 m–18 y C: 6 m–17 y	I: 32/32; 0 C: 28/28; 0	I: 38.6 y; 14/18 C: 39.2 y; 12/16	*Kang min ling he ji* (mixture): 30 ml tid, po	Ebastine: 10 mg qd, po
Wang YF 2011 (166)	NS; 2	28 d; NS	Total: 1.8 y	I: 60/60; 0 C: 60/60; 0	Total: 37 y; 62/58	*Fu yang ke li* (granules): nine g tid, po	Epinastine: 20 mg qd, po
Wang YJ 2011 (165)	NS; 2	4 w; 1 m	I: 3.8 (1.73) y C: 3.1 (1.56) y	I: 60/60; 0 C: 56/56; 0	I: 34.7 (11.3) y; 27/33 C: 31.8 (10.5) y; 25/31	Total glycosides of paeony (capsule): 0.6 g tid, po	Fexofenadine: 60 mg bid, po

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Wei X 2013 (164)	NS; 2	4 w; 4 w	NS	I: 41/41; 0	I: 34.5 (10.7) y; 20/21	*Yu ping feng jiao nang* (capsules): 1000 mg, tid po	Desloratadine: 8.8 mg qd, po
				C: 40/40; 0	C: 37.2 (12.9) y; 20/20		
Wu CY 2014 (189)	NS; 2	4 w; NS	I: 8.25 (2.11) m	I: 60/60; 0	I: 36.25 (18.35) y; 29/31	*Ma huang xi xin fu zi tang* (decoction): bid or tid, po	Desloratadine: 10 mg qd, po
			C: 8.45 (2.38) m	C: 60/60; 0	C: 37.15 (18.33) y; 28/32		
Wu GZ 2012 (200)	NS; 2	4 w; 4 w	I: 2.1 y	I: 80/80; 0	I: 33.94 y; 51/29	Unnamed formula (decoction): bid, po	Levocetirizine: 10 mg qd, po
			C: 2.3 y	C: 74/74; 0	C: 34.14 y; 48/26		
Wu YX 2007 (163)	NS; 2	28 d; NS	I: 12.5 (13.2) m	I: 33/33; 0	I: 44.7 (10.4); 12/21	*Xiao feng zhi yang ke li* (granules): 30 g bid, po	Loratadine: 10 mg qd, po
			C: 13.1 (14.3) m	C: 30/30; 0	C: 42.9 (11.6); 13/17		
Wu YX 2015 (198)	NS; 2	15 d; 1 m	Total: 6.26 (0.85) y	I: 93/93; 0	Total: 43.62 (3.05) y; 102/84	Compound glycyrrhizin (capsule): 50 mg tid, po	Mizolastine: 10 mg qd, po
				C: 93/93; 0			
Xiao HW 2010 (162)	NS; 2	4 w; 3 m	I: 2.5 y	I: 49/49; 0	I: 30.3 y; 28/21	*Yu ping feng ke li* (granules): 5 g tid, po	Epinastine: 10 mg qd, po
			C: 2.4 y	C: 32/32; 0	C: 32.8 y; 19/13		
Xu JJ 2014 (190)	NS; 2	8 w; 1 m	I: 1.2 y	I: 45/45; 0	I: 8.33 (2.27) y; 24/21	*Fu yang ke li* (granule): 6–12 g tid, po	Loratadine: 5 mg qd, po (≤30 kg); 10 mg qd, po (≥30 kg)
			C: 1.3 y	C: 41/41; 0	C: 7.75 (2.80) y; 23/18		

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Xue CL 2009 (100)★	NS; 3	30 d; NS	I: 5.24 y	I: 51/51; 0	I: 23.74 y; 23/28	*Kang man min jian* (decoction): 150 ml tid, po; cetirizine: used as control group per 2	C1: *Kang man min jian* (decoction): 150 ml tid, po; C2: cetirizine: 10 mg tid, po
			C1: 4.58 y	C1: 43/43; 0	C1: 24.25 y; 20/23		
			C2: 3.36 y	C2: 45/45; 0	C2: 22.16 y; 23/22		
Yang L 2011 (161)	NS; 2	4 w; 3 m	NS	I: 48/48; 0	Total: NS; NS	Tripterygium glycosides (tablets): 20 mg tid, po	Desloratadine: five mg qd, po
				C: 48/48; 0			
Yang MF 2014 (143)★	NS; 3	4 w; 4 w	I: 0.88 (0.26) y	I: 45/45; 0	I: 38.41 (4.05) y; 20/25	*Zhen qi fu zheng ke li* (granule): 15 g bid, po; levocetirizine: used as per control group	C1: Levocetirizine: five mg qd, po C2: *Zhen qi fu zheng ke li* (granule): 15 g bid, po
			C1: 1.01 (0.17) y	C1: 45/45; 0	C1: 41.65 (3.01) y; 23/22		
			C2: 0.98 (0.32) y	C2: 45/45; 0	C2: 40.51 (3.89) y; 20/25		
Yang YS 2014 (150)	NS; 2	12 w; NS	I: 6 w–1 y	I: 65/65; 0	I: 48.2 (10.2) y; 27/38	Total glycosides of paeony (capsule): 600 mg bid, po	Desloratadine: five mg qd, po
			C: 6 w–1 y	C: 65/65; 0	C: 44.5 (12.5) y; 25/40		
Ye WW 2009 (160)	NS; 2	6 w; 3 m	I: 7.6 y	I: 60/60; 0	I: 45.6 y; 37/23	*Di huang yin zi* (decoction): bid, po	Cetirizine: 10 mg qd, po
			C: 7.2y	C: 56/56; 0	C: 44.4 y; 30/26		
Yuan JQ 2013 (146)	NS; 2	4 w; NS	I: 2 m–2 y	I: 32/32; 0	I: 1–13 y; 18/14	*Xiao feng san* (decoction): bid, po	Desloratadine: 1.25 mg qd, po (age: 1–5 y); 2.5mg qd, po (age: 6–11 y); five mg qd, po (age: over 12 y)
			C: 3 m–2 y	C: 32/32; 0	C: 1–12 y; 20/12		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Zhang HB 2011 (159)	NS; 2	4 w; 1 m	NS	I: 43/43; 0	I: 34.6 (10.9) y; 24/19	*Qing feng tang* (decoction): qd, po	Setastine: one mg bid, po
				C: 43/43; 0	C: 37.1 (13.1) y; 18/25		
Zhang HX 2014 (191)	NS; 2	8 w; 4 w	I: 22.6 m	I: 30/30; 0	I: 36.8 y; 14/16	Total glycosides of paeony (capsule): 600 mg tid, po	Ebastine: 10 mg qd, po
			C: 25.2 m	C: 30/30; 0	C: 38.3 y; 13/17		
Zhang L 2014 (137)	NS; 2	4 w; NS	Total: 3 m–5 y	I: 56/56; 0	Total: 12–70 y; 54/58	Total glycosides of paeony (capsule): 600 mg tid, po	Mizolastine: 10 mg qd, po
				C: 56/54; 2			
Zhang Q 2011 (148)	NS; 2	7 d; 1 m	I: 6 m	I: 50/50; 0	I: 9 y or 4–12 y; 25/25	*Jia wei yu ping feng tang* (decoction): tid, po	Desloratadine: 1.25–5 mg qd, po
			C: NS	C: 50/50; 0	NS		
Zhang TL 2011 (158)	NS; 2	4 w; 8 w	I: 15 m	I: 44/44; 0	I: 26.8 y; 21/23	*Dang gui yin zi* (decoction): qd, po	Levocetirizine: five mg qd, po
			C: 14 m	C: 44/44; 0	C: 27.1 y; 22/22		
Zhao HW 2010 (157)	NS; 2	28 d; 1 m	I: 16.3 m	I: 80/80; 0	I: 35.8 y; 52/28	*Man xun tang* (decoction): 100 ml bid, po	Ebastine: 10 mg qd, po
			C: 16.3 m	C: 40/40; 0	C: 36.2 y; 26/14		
Zhao JH 2010 (156)	NS; 2	28 d; 2 w	I: 3m-5y	I: 88/88; 0	I: 35.1 y; 48/40	*Yu ping feng* (dripping pills): 2.4 g tid, po	Mizolastine: 10 mg qd, po
			C: 3 m–4.5 y	C: 84/84 ;0	C: 34.3 y; 46/38		
Zhao YY 2014 (192)	NS; 2	4 w; 2 m	I: 1 (0.3) y	I: 44/44; 0	I: 36.4 (9.5) y; 20/24	Total glycosides of paeony (capsule): 600 mg tid, po	Fexofenadine: 120 mg qd, po
			C: 1.2 (0.45) y	C: 47/47; 0	C: 35.3 (8.7) y; 21/26		

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Zhao ZY 2004 (152)	NS; 2	3 w; 3 m	I: 2.6 y C: 2.8 y	I: 42/42; 0 C: 40/40; 0	I: 44.5 y; 23/19 C: 45.6 y; 21/19	*Yong an zhi yang ke li* (granule): 3 g bid or tid, po	Mizolastine: 10 mg qd, po
Zheng Y 2008 (155)	NS; 2	28 d; 4 w	Total: 4.3 y	I: 51/51;0 C: 47/47; 0	Total: 27.4 y; 40/58	Urticaria basic formula (modified decoction): bid, po	Cetirizine: 10 mg qd, po
Zheng ZY 2014 (193)	NS; 2	2 w; NS	I: 6 w–2.5 y C: 6 w–2.3 y	I: 41/41; 0 C: 38/38; 0	I: 30.5 y; 24/17 C: 31.2 y; 23/15	Compound glycyrrhizin (capsule): 50 mg tid, po	Fexofenadine: 60 mg bid, po
Zhong JQ 2011 (138)	PRA-B; 2	4 w; 20 w	I: 67 (13-361) w C: 65 (9-312) w	I: 40/37; 3 C: 38/32; 6	I: 36 (21–58); 19/21 C: 35 (23–56); 20/18	Tripterygium hypoglaucum Hutch (tablet): three tablets tid, po; cetirizine: used as control group	Placebo: used as intervention group; cetirizine: 10 mg qd, po
Zhong X 2005 (153)	NS; 2	14 d; 3 m	I: 2.3 (1.4) y C: 2.5 (1.6) y	I: 51/51; 0 C: 48/48; 0	I: 27.4 (12.5) y; 27/24 C: 26.7 (11.4) y; 26/22	*Yi qi yang xue huo xue qu feng tang* (decoction): bid, po	Mizolastine: 10 mg qd, po
Zhou JW 2011 (199)	NS; 2	15 d; NS	Total: NS	I: 35/35; 0 C: 35/35; 0	I: 34.64 (3.31) y; 20/15 C: 34.74 (2.24) y or 13–64 y; 21/14	*Ma huang fu zi xi xin tang* (decoction): tid, po	Loratadine: 10 mg qd, po
Zhou L 2012 (147)	NS; 2	30 d; 3 w	I: 3.5 y C: 3.6 y	I: 30/30; 0 C: 30/30; 0	I: 38 y; 16/14 C: 37.5 y; 18/12	*Yi qi huo xue qu feng tang* (decoction): bid, po	Mizolastine: 10 mg qd, po
Zhu JF 2012 (154)	NS; 2	4 w; 3 m	1.79 (0.62) y	I: 82/82; 0 C: 82/82; 0	Total: 35.87 (8.38) y; 87/77	Compound glycyrrhizin (capsule): 50 mg tid, po	Cetirizine: 10 mg qd, po

First author, publication year	Blinding; number of arms	Treatment duration; follow-up duration	Duration of condition (mean [SD] or range)	No. of participants randomised/ assessed; dropouts	Age (mean [SD] or range); gender (M/F)	Intervention	Control
Zhuang Q 2011 (179)	NS; 2	8 w; 2 m	I: 15.91 (3.23) m	I: 36/30; 7	I: 36.82 (13.26) y; 15/15	*Xiao chai hu tang* (decoction): bid, po	Mizolastine: 10 mg qd, po
			C: 13.49 (4.59) m	C: 36/30; 5	C: 34.58 (14.97); 16/14		

Notes: * Formula name not stated, formula based on Chinese medicine treatment principle; ★ study with three or more arms; C: Control; I: Intervention; m: months; mg: milligram; ml: milliliter; NS: not stated; po: administrated orally; PRA-B: all blinded; qd: once daily; qn: once per night; tid: three times daily; w: weeks, y: years;

Table 7.2: Details of Chinese Herbal Medicine formula: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria

First author publication year	Ingredients of CHM
Bai WJ 2011 (177)	*Xiao feng san: huang qi, fang feng, bai zhu, dan shen, dang gui, mu dan pi, sheng di huang, shu di huang, chan yi, ku shen, gan cao*
Bao LX 2008 (176)	*Tripterygium glycosides:* NS
Chen CS 2015 (194)	*Yu ping feng ke li* (granule)*: huang qi, bai zhu, fang feng*
Chen JY 2014 (181)	*Xiao yin ke li* (granule): NS
Chen XB 2011 (145)	Unnamed formula*: sheng di huang, qin jiao, xu chang qing, fu ping, yi yi ren, chan tui, gan cao*
Cheng Y 2010 (175)	*Ba zhen san plus si wu xiao feng san: fu ling, bai zhu, jing jie, fang feng, chan tui, niu bang zi, cang zhu, ku shen, dang gui, sheng di, chi shao, chuan xiong, bo he, sheng gan cao*
Deng D 2012 (174)	*Pi min xiao jiao nang* (capsule)*: ku shen, cang zhu, fang feng, jing jie, ji li, bai xian pi, she chuang zi, cang er zi, wu gong, qing dai, pu gong ying, zi hua di ding, huang qin, huang bo, huang lian, di huang, mu dan pi, chan tui, xi he liu, zi cao, di gu pi*
Ding QY 2007 (173)	*Run zao zhi yang jiao nang* (capsule): *sheng di huang, he shou wu, zhi he shou wu, sang ye, ku shen, hong huo ma,* (etc.)
Feng S 2015 (195)	*Qu feng qing re wei ling tang: huang qin, lian qiao, chen pi, fa ban xia, bai zhu, jing jie, fang feng, ku shen, bai xian pi, huang bo, zhi zi, fu ling, zhu ling, cang shu, gan cao, sheng ma*
Fu YH 2011 (141)*	1. Fortifying the Spleen and nourishing Blood: *huang qi, da zao, shan yao, fu ling, dang gui, zhi shou wu* 2. Dispelling wind: *jing jie, fang feng, chan tui, niu bang zi, hu ma ren, ci ji li*
Guo XY 2014 (182)	Compound glycyrrhizin: NS
Huang SY 2012 (206)	*Guo min jian: yin chai hu, fang feng, wu mei, wu wei zi, gan cao*
Jiang YP 2009 (172)	*Qi feng ke li* (granules)*: huang qi, fang feng, bai zhu, fu ling, chen pi, gui zhi, da fu pi, sang bai pi, (etc.)*
Jiang YP 2011 (151)	Compound glycyrrhizin: NS
Jie SH 2014 (135)	Total glycosides of paeony: NS
Leng J 2014 (136)	*Run zao zhi yang jiao nang* (capsule)*: sheng di huang, he shou wu, zhi he shou wu, sang ye, ku shen, huo hong ma,* (etc.)
Li CH 2014 (183)	*Yu ping feng ke li (granule): huang qi, bai zhu, fang feng*
Li ZL 2013 (171)	*Qing re xiao feng san: jing jie, niu bang zi, chan tui, fang feng, sheng di huang, dang gui, hong hua, mu dan pi, zi cao, jiang can, dan zhu ye, gan cao*
Liao C 2014 (184)	*Yu ping feng ke li (granule): huang qi, bai zhu, fang feng*

First author publication year	Ingredients of CHM
Lin YP 2012 (149)	Total glycosides of paeony: NS
Lin ZF 2014 (142)	*Yu ping feng ke li* (granule): *huang qi, bai zhu, fang feng*
Liu Y 2014 (185)	*Fu fang di fu zi tang: di fu zi, huai mi, sang bai pi, chan tui,* (etc.)
Long JW 2010 (139)	Total glycosides of paeony: NS
Lu JM 2007 (180)	*Qu feng xiao zhen tang: fang feng, chan tui, jiang can, xu chang qing, dan shen, dang gui, bai xian pi, bai ji li, di fu zi*
Lu XY 2010 (205)	*Yu ping feng san* (modified)*: fang feng, huang qi, bai zhu, jing jie, chai hu, bai shao, dang gui, bai xian pi, chan tui, tu fu ling, mu dan pi, lian qiao, gan cao*
Ma LB 2012 (170)	*Qi feng ke li* (granules): *huang qi, fang feng, bai zhu, fu ling, chen pi, gui zhi, da fu pi, sang bai pi,* (etc.)
Ma WH 2010 (169)	*Wu she zhi yang wan* (pills)*: wu qiao she, fang feng, she chuang zi, huang bo, cang zhu, ren shen xu, mu dan pi, she dan juice, ku shen, man-made niu huang, dang gui*
Ma XM 2013 (178)	*Yu ping feng san: huang qi, fang feng, bai zhu*
Mei T 2014 (186)	*Yu ping feng jiao nang* (capsule): NS
Mi L 2008 (204)	*Jia wei yang he tang: shu di huang, ma huang, lu jiao jiao, bai jie zi, rou gui, sheng gan cao, pao tan jiang, bai shao, bai xian pi*
Mou Y 2011 (168)	Total glycosides of paeony: NS
Qian M 2011 (140)	Tripterygium glycosides: NS
Shi CR 2013 (99)	*Dang gui yin zi: dang gui, bai shao, chuan xiong, sheng di huang, bai ji li, fang feng, jing jie, he shou wu, huang qi, zhi gan cao*
Song SH 2015 (144)	*Xiao yin fang: fang feng, chan tui, bai xian pi, di fu zi, ye jiao teng, huang qi, dang gui, mu dan pi, ci ji li, dan shen, shan yao, sheng gan cao*
Sun H 2015 (196)	*Qu feng kang min jian: huang qi, dang gui, bai zhu, bai shao, fang feng, yin chai hu, wu mei, jing jie, wu wei zi, gan cao*
Sun RF 2007 (203)	Unnamed formula: *sheng di huang, bai shao, dang gui, chuan xiong, huang qi, fu ling pi, jing jie, fang feng, bai zhu, dang shen, ci ji li, sheng gan cao*
Sun RH 2014 (187)	*Run zao zhi yang jiao nang* (capsule): *sheng di huang, he shou wu, zhi he shou wu, sang ye, ku shen, hong huo ma,* (etc.)
Sun RL 2014 (188)	Total glycosides of paeony: NS
Tian AP 2011 (202)	*Fang ci yin hua fang: fang feng, ci ji li, jin yin hua, shou wu teng, bai xian pi, dang gui, mu dan pi, fu ping, chan tui,* gan cao
Tian J 2015 (197)	Compound glycyrrhizin: NS

First author publication year	Ingredients of CHM
Wang N 2011 (167)	*Si wu xiao feng san: jing jie, fang feng, chi shao, chuan xiong, dang gui, sheng di huang, cang zhu, bai xian pi, di fu zi*
Wang NL 2010 (201)	*Kang min ling he ji* (mixture)*: dang gui, da zao, dang shen, huang qi, gui zhi, ma huang, jing jie, gan cao,* (etc.)
Wang YF 2011 (166)	*Fu yang ke li* (granules)*: cang er zi, di fu zi, hong hua, chuan xiong, bai ying,* (etc.)
Wang YJ 2011 (165)	Total glycosides of paeony: NS
Wei X 2013 (164)	*Yu ping feng jiao nang* (capsules): NS
Wu CY 2014 (189)	*Ma huang xi xin fu zi tang: ma huang, xi xin, chan tui, lu jiao shuang, dang gui, huang qi, he shou wu*
Wu GZ 2012 (200)	Unnamed formula: *huang qi, chi shao, dang shen, dang gui, lian qiao, huang bo, jing jie, di fu zi, chen pi, gan cao*
Wu YX 2007 (163)	*Xiao feng zhi yang ke li (granules): fang feng, jing jie, sheng di huang, di gu pi, dang gui, chan tui, cang zhu, shi gao, mu tong, gan cao*
Wu YX 2015 (198)	Compound glycyrrhizin: NS
Xiao HW 2010 (162)	*Yu ping feng ke li* (granules): NS
Xu JJ 2014 (190)	*Fu yang ke li* (granule): *di fu zi, cang er zi, chuan xiong, hong hua, bai ying* (etc.)
Xue CL 2009 (100)	*Kang man min jian: chai hu, bai shao, fang feng, chan tui, di long, bai xian pi, tu fu ling, lian qiao, mu dan pi, huang qi, dang shen, bai zhu, dang gui, gan cao*
Yang L 2011 (161)	Tripterygium glycosides: NS
Yang MF 2014 (143)	*Zhen qi fu zheng ke li* (granule): *huang qi, nv zhen zi*
Yang YS 2014 (150)	Total glycosides of paeony: NS
Ye WW 2009 (160)	*Di huang yin zi: shu di huang, ba ji tian, shan zhu yu, shi hu, rou cong rong, fu zi, wu wei zi, rou gui, bai fu ling, mai men dong, shi chang pu, yuan zhi, sheng jiang, da zao, bo he, (etc.)*
Yuan JQ 2013 (146)	*Xiao feng san: jing jie, fang feng, niu bang zi, chan tui, cang shu, ku shen, duan shi gao, zhi mu, dang gui, hu ma ren, sheng di huang, gan cao*
Zhang HB 2011 (159)	*Qing feng tang: sheng huang qi, jing jie, fang feng, chan tui, zi bei fu ping, bai ji li, bai shu, bai shao, gan cao, dang gui, sheng di huang, chuan xiong, wu wei zi*
Zhang HX 2014 (191)	Total glycosides of paeony: NS
Zhang L 2014 (137)	Total glycosides of paeony: NS
Zhang Q 2011 (148)	*Jia wei yu ping feng tang: huang qi, bai zhu, fang feng, jing jie, gan cao, di fu zi, huang qin, fu ling, shan zha, chen pi*

First author publication year	Ingredients of CHM
Zhang TL 2011 (158)	*Dang gui yin zi: dang gui, chuan xiong, bai shao, sheng di huang, fang feng, bai ji li, jing jie, he shou wu, huang qi, gan cao*
Zhao HW 2010 (157)	*Man xun tang: huang qi, bai shu, fang feng, jing jie, sheng di huang, dang gui, dan shen, chuan xiong, chi shao, ma huang, gui zhi, ye jiao teng, bai ji li, bai jiang can, gan cao, fu ping, ma chi xian*
Zhao JH 2010 (156)	*Yu ping feng* (dripping pills): *fang feng, huang qi, bai shu*
Zhao YY 2014 (192)	Total glycosides of paeony: NS
Zhao ZY 2004 (152)	*Yong an zhi yang ke li* (granule)*: ma huang, jing jie, fang feng, cang zhu, jiang can, tao ren, hong hua, chi shao, dang gui*
Zheng Y 2008 (155)	*Urticaria basic formula* (modified decoction)*: huang qi, bai shu, dang gui, chi shao, jing jie, fang feng, chan tui, bai xian pi, zi cao, mu dan pi, huang qin, gan cao*
Zheng ZY 2014 (193)	Compound glycyrrhizin: NS
Zhong JQ 2011 (138)	*Tripterygium hypoglaucum* Hutch: NS
Zhong X 2005 (153)	*Yi qi yang xue huo xue qu feng tang: huang qi, bai zhu, chuan xiong, dang gui, zhi he shou wu, sheng di huang, chi shao, jing jie, fang feng, di fu zi, bai xian pi, chan tui, mu dan pi*
Zhou JW 2011 (199)	*Ma huang fu zi xi xin tang: ma huang, shu fu zi, xi xin, gui zhi, bai shao, gan cao, sheng jiang, da zao*
Zhou L 2012 (147)	*Yi qi huo xue qu feng tang: huang qi, dang gui, chuan xiong, sheng di huang, chi shao, shou wu, jing jie, fang feng, ji xue teng, chan tui*
Zhu JF 2012 (154)	Compound glycyrrhizin: NS
Zhuang Q 2011 (179)	*Xiao chai hu tang: chai hu, ban xia, dang shen, huang qin, sheng jiang, da zao, gan cao*

* Formula name not stated, formula based on Chinese medicine treatment principle; NS not stated

7.3.2 Outcome Measures

UAS was used in four studies (99, 140, 181, 184) to assess disease activity, but only one study reported actual scores (140). The other study reported UAS percentage score change from baseline (99), and two studies reported the number of participants who achieved UAS changes of 30% or more after receiving treatments (181, 184). This is not consistent with the prescribed use of the outcome measure UAS. All studies reported on ER and two approaches were used to calculate this (see Chapter 5). ER 30 was reported in 13 studies (100, 145, 148, 152, 153, 199–206) and SSRI 30 was used in the remaining studies. Relapse rate, based on ER 30, was reported in two studies (152, 153). DLQI was used in one study to assess participants' HR-QoL. AEs were reported in all but 22 studies (100, 145, 148, 151–154, 161, 167, 171, 174, 179, 184, 189, 194, 196, 198, 200, 201, 204, 206).

7.3.3 Risk of Bias Assessment

While all studies claimed that participants were randomly allocated, only 12 studies described the appropriate methods of random sequence generation (99, 138, 139, 141, 157, 178, 186, 189, 190, 192, 195, 197) (see Table 7.3). Three studies used a computer to generate random numbers (99, 138, 141), eight studies used a random number table to allocate participants (157, 178, 186, 189, 190, 192, 195, 197) while lottery was used in one study (139). These 12 studies were judged as low risk for sequence generation (see Table 7.3). Eleven studies were assessed as high risk for generation of allocation sequence (147, 151–153, 156, 161, 166, 171, 173, 179, 206), while six studies allocated participants based on the order of visiting (147, 156, 166, 171, 173, 179). Participants could select their group allocation in two studies (152, 153) and randomisation was only mentioned in the abstracts of three studies (151, 161, 206).

The remaining studies did not provide detailed prescriptions for sequence generation and were judged to pose an unclear risk. In relation to allocation concealment, eight studies were assessed as high risk since research personnel or participants could predict the treatments (147, 152, 153, 156, 166, 171, 173, 179). Six of these studies determined participants' allocations based on visiting order (147, 156, 166, 171, 173, 179) and two studies allowed participants to choose (152, 153). All remaining studies were considered to carry unclear risk for allocation concealment due to lack of information. Participants and researchers involved in one study (138) were blinded. Therefore, this study was judged as low risk for all the blinding domains. The remaining studies did not use methods to blind participants and personnel to group allocation; thus, they were judged as high risk. In terms of blinding outcome assessors, except for Zhong (2011) (138), all studies were assessed as unclear risk due to lack of information. Three studies (139, 142, 179) were deemed an unclear risk for incomplete outcome data. Two (142, 179) reported the number of withdrawals and dropouts in both groups but did not discuss reasons. Another study (139) reported an imbalance in the numbers and reasons for withdrawal. However, it was unable to be determined if this was related to the true outcome. Intention-to-treat (ITT) analysis was not used to manage the data in these three studies (139, 142, 179). The remaining studies were considered at low risk of bias since all outcome data were available. Protocols and registration information could not be identified for all studies. Further, three studies (147, 156, 179) did not report the results of outcomes mentioned in the 'method' section of the articles. These studies (147, 156, 179) were judged as high risk for selective outcome reporting and the rest of studies were unclear risk (see Table 7.3).

Table 7.3: Risk of Bias Assessment Results: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria

First author, publication year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
Bai WJ 2011 (177)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Bao LX 2008 (176)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Chen CS 2015 (194)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Chen JY 2014 (181)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Chen XB 2011 (145)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Cheng Y 2010 (175)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Deng D 2012 (174)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Ding QY 2007 (173)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Feng S 2015 (195)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Fu YH 2011 (141)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Guo XY 2014 (182)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Huang SY 2012 (206)	High risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Jiang YP 2009 (172)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Jiang YP 2011 (151)	High risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Jie SH 2014 (135)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Leng J 2014 (136)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Li CH 2014 (183)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Li ZL 2013 (171)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Liao C 2014 (184)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Lin YP 2012(149)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Lin ZF 2014 (142)	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	Unclear
Liu Y 2014 (185)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Long JW 2010 (139)	Low risk	Unclear	High risk	Unclear	Unclear	Unclear	Unclear
Lu JM 2007 (180)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Lu XY 2010 (205)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Ma LB 2012 (170)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear

First author, publication year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
Ma WH 2010 (169)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Ma XM 2013 (178)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Mei T 2014 (186)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Mi L 2008 (204)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Mou Y 2011 (168)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Qian M 2011 (140)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Shi CR 2013 (99)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Song SH 2015 (144)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Sun H 2015 (196)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Sun RF 2007 (203)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Sun RH 2014 (187)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Sun RL 2014 (188)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Tian AP 2011 (202)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Tian J 2015 (197)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Wang N 2011 (167)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wang NL 2010 (201)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wang YF 2011 (166)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Wang YJ 2011 (165)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wei X 2013 (164)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wu CY 2014 (189)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Wu GZ 2012 (200)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wu YX 2007 (163)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Wu YX 2015 (198)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Xiao HW 2010 (162)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Xu JJ 2014 (190)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Xue CL 2009 (100)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yang L 2011 (161)	High risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yang MF 2014 (143)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Yang YS 2014 (150)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear

First author, publication year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
Ye WW 2009 (160)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Yuan JQ 2013 (146)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang HB 2011 (159)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang HX 2014 (191)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Zhang L 2014 (137)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Zhang Q 2011 (148)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhang TL 2011 (158)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhao HW 2010 (157)	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhao JH 2010 (156)	High risk	High risk	High risk	High risk	Unclear	Low risk	High risk
Zhao YY 2014 (192)	Low risk	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Zhao ZY 2004 (152)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Zheng Y 2008 (155)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zheng ZY 2014 (193)	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear
Zhong JQ 2011 (138)	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Zhong X 2005 (153)	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear
Zhou JW 2011 (199)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhou L 2012 (147)	High risk	High risk	High risk	High risk	Unclear	Low risk	High risk
Zhu JF 2012 (154)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Zhuang Q 2011 (179)	High risk	High risk	High risk	High risk	Unclear	Unclear	High risk

7.3.4 Effects of the Intervention

Urticaria Activity Score

Four studies used UAS to assess disease activity (99, 140, 181, 184). As add-on therapy to second-generation antihistamine, one study indicated that CHM reduced UAS score by 0.45 points at the end of treatment when compared with second-generation antihistamine alone ([-0.58, -0.32]) (140). One study reported UAS percentage score change from baseline (99). Statistical difference was not found between groups (MD: 0.14 [-0.25, 0.53]). The remaining two studies (181, 184) reported the number of participants who achieved UAS score changes of 30% or higher after receiving treatments. When the data were pooled, CHM as add-on therapy did not increase the number of participants achieving UAS score improvements of 30% or higher when compared with antihistamines (RR: 1.16 [1.00, 1.35], $I^2 = 15\%$, $p = 0.05$).

Effective Rate 30

The data of ER 30 from 13 studies (100, 145, 148, 152, 153, 199–206) were pooled to evaluate the effects of CHM as add-on therapy to antihistamines. The results showed that CHM could provide additional benefits in improving chronic urticaria symptoms by 30% or more compared with antihistamines alone (RR: 1.19 [1.10, 1.27], $I^2 = 54\%$) (see Table 7.4).

Sensitivity and subgroup analyses were conducted to explore the substantial statistical heterogeneity (54%) (see Table 7.4). As none of the studies reporting ER 30 were assessed as low risk bias for sequence generation, an alternative method was used to explore statistical heterogeneity. After excluding studies judged as high risk of bias for sequence generation, sensitivity analysis involving 11 studies still found CHM as an add-on therapy favourable and

reduced the statistical heterogeneity to 33%. Subgroup analysis according to the various antihistamine agents suggested that CHM as an add-on therapy increased the number of participants achieving improvement in symptoms by 30% or more compared with cetirizine (RR: 1.20 [1.08, 1.33], I^2 = 0%), and levocetirizine (RR: 1.27 [1.09, 1.49], I^2 = 63%). The statistical heterogeneity was removed when cetirizine was used as co-intervention and comparator, but remained substantial when levocetirizine was applied. Statistical difference was not found in comparison with loratadine (RR: 1.35 [0.79, 2.31], I^2 = 74%) or mizolastine (RR: 1.06 [0.99, 1.15], I^2 = 0%).

Table 7.4: Effect Size Analysis: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria: ER 30

Subgroup	No. of studies	No. of cases analysed (I/C)	Effect estimate (RR, 95% CI, I^2)	References
NA	13	601/576	1.19 [1.10, 1.27], 54 %	(100, 145, 148, 152, 153, 199-206)
Sensitivity analysis: excluding high RoB SG	11	508/488	1.22 [1.14, 1.31], 33 %	(100, 145, 148, 199-206)
Cetirizine	3	121/115	1.20 [1.08, 1.33], 0 %	(100, 204, 206)
Loratadine	2	70/70	1.35 [0.79, 2.31], 74 %	(145, 199)
Levocetirizine	4	235/225	1.27 [1.09, 1.49], 63 %	(200, 202, 203, 205)
Mizolastine	2	93/88	1.06 [0.99, 1.15], 0%	(152, 153)

Notes: C: comparator; CHM: Chinese herbal medicine; CI: confidence interval; ER 30: effective rate based on Chinese Medicine guideline; I: intervention; NA: not applicable; RR: risk ratio; RoB: risk of bias assessment; SG: sequence generation

Symptom Severity Reduction Index 30

CHM as an add-on therapy also improved the outcome SSRI 30. Meta-analysis of 57 studies showed that additional CHM increased the number of participants who achieved an improvement in symptoms of 30% or more when compared with antihistamine alone (RR: 1.19 [1.14, 1.24], I^2 = 80%) (see Table 7.5). Again, sensitivity and subgroup analyses were conducted due to high statistical heterogeneity (80%). Studies deemed at low risk of bias for sequence generation were included to perform sensitivity analysis. Although the effect size increased, the statistical heterogeneity was still high (RR: 1.27 [1.12, 1.44], I^2 = 85%) (see Table 7.5).

As most of the included studies adhered to a treatment duration of four weeks, subgroup analysis of this treatment duration was performed (see Table 7.5). No noteworthy change was observed in the amount of statistical heterogeneity (RR: 1.16 [1.10, 1.22], I^2 = 80%). Subgroup analysis by comparators found CHM as an add-on therapy increased the chance of achieving SSRI 30 when compared with cetirizine (RR: 1.27 [1.12, 1.43], I^2 = 75%) and levocetirizine (RR: 1.14 [1.04, 1.24], I^2 = 41%). The statistical heterogeneity of both groups decreased, especially the levocetirizine group, with an acceptable level. No statistical difference was found between CHM as an add-on therapy and loratadine groups, and heterogeneity increased (RR: 1.29 [0.97, 1.74], I^2 = 89%).

Table 7.5: Effect Size Analysis: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria: SSRI 30

Subgroup	No. of studies	No. of cases analysed (I/C)	Effect estimate (RR, 95% CI, I^2)	References
NA	57	2981/2781	1.19 [1.14, 1.24], 80 %	(99, 139–144, 146, 147, 149-151, 154–198)
Sensitivity analysis: Low RoB SG	11	493/347	1.27 [1.12, 1.44], 85 %	(99, 139, 141, 157, 178, 186, 189, 190, 192, 195, 197)
Cetirizine	11	577/539	1.27 [1.12, 1.43], 75 %	(99, 139, 141, 149, 154, 155, 160, 172, 180, 183, 184)
Loratadine	5	194/187	1.29 [0.97, 1.74], 89 %	(163, 175, 177, 190, 195)
Levocetirizine	4	202/199	1.14 [1.04, 1.24], 41 %	(142, 143, 158, 173)
Treatment duration four weeks/one month	37	1965/1812	1.16 [1.10, 1.22], 80 %	(99, 139, 140, 143, 144, 146, 147, 154–159, 161-167, 169, 170, 172–176, 178, 180–185, 189, 192, 197)

Notes: C: comparator; CHM: Chinese herbal medicine; CI: confidence interval; I: intervention; MD: mean difference; NA: not applicable; RR: risk ratio; RoB: risk of bias assessment; SG: sequence generation; SSRI 30: effective rate based on Symptom Severity Reduction Index

In addition to the consideration of comparators and treatment duration, subgroup analysis was performed according to the frequently used CHM formula or compound products (see Table 7.6). Most CHM formulae or compound products provided additional benefits to antihistamines in achieving SSRI 30, such as *Yu ping feng san* 玉屏风散 (RR: 1.13 [1.06, 1.20], I^2 = 34%), CG (from *gan cao* 甘草) 复方甘草酸苷 (RR: 1.11 [1.01, 1.22], I^2 = 68%) and *Dang gui yin zi* 当归饮子 (RR: 1.28 [1.05, 1.56], I^2 = 0%). No statistical difference was observed when *Xiao feng san* 消风散 (RR: 1.05 [0.86, 1.29], I^2 = 31%) and *Qi feng* granules 芪风颗粒 (RR: 1.06 [0.83, 1.36], I^2 = 91%), as add-on therapies, were compared with antihistamines. Substantial statistical heterogeneity was still detected in more than half of the subgroups.

Table 7.6: Effect Size Analysis: Individual Chinese Herbal Medicine Formulae as Add-on Therapy v. Antihistamines for Chronic Urticaria: SSRI 30

CHM formula	No. of studies	No. of cases analysed (I/C)	Effect estimate (RR, 95% CI, I^2)	References
Compound glycyrrhizin capsules	6	354/328	1.11 [1.01, 1.22], 68 %	(151, 154, 182, 193, 197, 198)
Dang gui yin zi	2	66/68	1.28 [1.05, 1.56], 0 %	(99, 158)
Qi feng granules	2	119/105	1.06 [0.83, 1.36], 91 %	(170, 172)
Total glycosides of peony	8	406/377	1.20 [1.01, 1.43], 84 %	(139, 149, 150, 165, 168, 188, 191, 192)
Tripterygium glycosides	3	319/304	1.32 [1.10, 1.58], 69 %	(140, 161, 176)
Xiao feng san	2	66/66	1.05 [0.86, 1.29], 31 %	(146, 177)
Yu ping feng san	9	438/412	1.13 [1.06, 1.20], 34 %	(142, 156, 162, 164, 178, 183, 184, 186, 194)

Notes: CHM: Chinese herbal medicine; CI: confidence interval; MD: mean difference; RR: risk ratio; SSRI 30: effective rate based on Symptom Severity Reduction Index

Relapse rate

The pooled data of two studies (152, 153) indicated that CHM as an add-on therapy reduced the risk of relapse (relapse rate) in comparison with antihistamines (RR: 0.27 [0.14, 0.54], $I^2 = 0\%$).

Dermatology Life Quality Index

The outcome related to QoL was reported in one study. Additional CHM improved the DLQI score of participants with chronic urticaria by 0.68 points when compared with antihistamines (MD: -0.68 [-0.92, -0.44]) (140).

7.3.5 Adverse Events

Most studies reported AEs except for 22 studies (100, 145, 148, 151–154, 161, 167, 171, 174, 179, 184, 186, 189, 194, 196, 198, 200, 201, 204, 206). Among these studies, seven studies reported no AEs (158, 162, 177, 183, 199, 202, 205) and five mentioned the nature of the events without specifying the number of AEs (135, 137, 138, 146, 165). The frequencies of AEs were calculated in the remaining studies. The number of AEs in participants who received CHM combined with antihistamine was 249, which was slightly higher than AEs reported for antihistamine use alone (228). The most commonly observed AEs in the add-on therapy group were somnolence (96 cases), gastrointestinal events (71 cases), dry mouth (17 cases) and dizziness (nine cases). AEs in the antihistamine group included somnolence (93 cases), dry mouth (45 cases), dizziness (18 cases), gastrointestinal events (16 cases) and fatigue (14 cases). Gastrointestinal events mainly involved diarrhoea, stomach discomfort and nausea, and were more frequently reported in participants who received CHM (see Table 7.7).

7.3.6 Publication Bias

Potential publication bias should be noted for ER 30 (13 studies) and SSRI 30 (57 studies) since the funnel plots showed asymmetry in the distribution of studies (see Figures 7.2 and 7.3).

Table 7.7: Adverse Events of Included Randomised Controlled Trials: Chinese Herbal Medicine as Add-on Therapy v. Antihistamines for Chronic Urticaria

First author, publication year	Adverse events
Bai WJ 2011 (177)	None
Bao LX 2008 (176)	I: Dry mouth (7), somnolence (7), fatigue (7), gastrointestinal discomfort (2), menstruation deferred (2). C: dry mouth (5), somnolence (5), fatigue (5)
Chen CS 2015 (194)	NS
Chen JY 2014 (181)	I: Somnolence (2), stomach discomfort (2). C: dizziness (1)
Chen XB 2011 (145)	NS
Cheng Y 2010 (175)	I: Somnolence (3), dry mouth (1), nausea (1), poor appetite (1). C: somnolence (4), dry mouth (1)
Deng D 2012 (174)	NS
Ding QY 2007 (173)	I: Somnolence (3), dizziness (1). C: dizziness (2), dry mouth (5), constipation (2)
Feng S 2015 (195)	I: Dizziness and lack of strength (1), dry mouth (1). C: somnolence (1)
Fu YH 2011 (141)*	I: Diarrhoea (1), abdominal pain (1), somnolence (4), headache (2), nausea (1). C1: Dry mouth (2), somnolence (5), fatigue (3), headache (2). C2: dry mouth (1), diarrhoea (1). C3: dry mouth (2), diarrhoea (2), abdominal pain (1)
Guo XY 2014 (182)	Somnolence (16)
Huang SY 2012 (206)	NS
Jiang YP 2009 (172)	I: Somnolence (2), dizziness (1). C: dizziness (2), dry mouth (3)
Jiang YP 2011 (151)	NS
Jie SH 2014 (135)	Abdominal discomfort (NS)
Leng J 2014 (136)	I: Somnolence and dizziness (1). C: dry month (4), constipation (2)
Li CH 2014 (183)	None
Li ZL 2013 (171)	NS
Liao C 2014 (184)	NS
Lin YP 2012 (149)	I: Diarrhoea (3), somnolence (1). C: somnolence (2)
Lin ZF 2014 (142)	I: Somnolence, dizziness, tired and inattention (6). C: somnolence, dizziness, tired and inattention (7)
Liu Y 2014 (185)	I: Dizziness (1), mild swelling of lower limbs (1). C: dizziness (2), mild swelling of lower limbs (1), feel hot (1)
Long JW 2010 (139)	I: Drowsiness, dizziness and weakness (8), mild diarrhoea (2). C: drowsiness, dizziness and weakness (7)
Lu JM 2007 (180)	I: Abdominal discomfort (3), poor appetite (3). C: dry mouth (4), fatigue (4)
Lu XY 2010 (205)	None

First author, publication year	Adverse events
Ma LB 2012 (170)	I: Somnolence (9), dry mouth (2). C: somnolence (6), dry mouth (4), dizziness (2), constipation (2)
Ma WH 2010 (169)	I: Somnolence (2), dry mouth (2). C: somnolence (2), headache (2)
Ma XM 2013 (178)	I: Nausea, stomach discomfort (3). C: dry mouth (2), fatigue (1), increased appetite (1)
Mei T 2014 (186)	NS
Mi L 2008 (204)	NS
Mou Y 2011 (168)	Total: Somnolence (5)
Qian M 2011 (140)	I: Nausea and vomiting (4), dizziness (3), insomnia (3), palpitation (3), hair loss (3). C: somnolence (C3:4, C2:3), dizziness (C3:1), body discomfort (C3:1)
Shi CR 2013 (99)	I: None. C1: dizziness (1), somnolence (1). C2: Diarrhoea (2)
Song SH 2015 (144)	I: Somnolence and headache (3), diarrhoea (2). C1: somnolence (3), headache and dizziness (2), liver function index slightly higher (1). C2: Loose stool and abdominal discomfort (3), nausea (1)
Sun H 2015 (196)	NS
Sun RF 2007 (203)	I: Somnolence (3), stomach discomfort (1), dry mouth (1). C: somnolence (4), stomach discomfort (1), dry mouth (2)
Sun RH 2014 (187)	I: Dizziness (1), dry month (1), somnolence and lack of strength (2). C: dry month (3), somnolence (3), gastrointestinal discomfort (2), constipation (3)
Sun RL 2014 (188)	I: Diarrhoea (2). C: somnolence, lack of strength and dry mouth (1)
Tian AP 2011 (202)	None
Tian J 2015 (197)	I: Somnolence, slow reaction, dizziness (3). C: somnolence, slow reaction, dizziness (4)
Wang N 2011 (167)	NS
Wang NL 2010 (201)	NS
Wang YF 2011 (166)	I: Somnolence (3), gastrointestinal discomfort (2). C: somnolence (2), dry mouth (4), constipation (2)
Wang YJ 2011 (165)	Somnolence (NS), headache (NS), nausea (NS)
Wei X 2013 (164)	I: Dizziness and fatigue (2), dry mouth (1). C: dizziness (1), somnolence (1)
Wu CY 2014 (189)	NS
Wu GZ 2012 (200)	NS
Wu YX 2007 (163)	I: Somnolence (2), headache (3), stomach discomfort (1), diarrhoea (1). C: somnolence (3), dizziness (2), dry mouth (2), fatigue (1)
Wu YX 2015 (198)	NS
Xiao HW 2010 (162)	None
Xu JJ 2014 (190)	I: Somnolence (2), dry mouth (1). C: somnolence (1), dry month (2), constipation (1)

First author, publication year	Adverse events
Xue CL 2009 (100)	NS
Yang L 2011 (161)	NS
Yang MF 2014 (143)	I: Somnolence (3), headache (2). C1: somnolence (3), hiccups (3), nausea (1). C2: NS
Yang YS 2014 (150)	I: Diarrhoea (20), somnolence (4). C: somnolence (6)
Ye WW 2009 (160)	I: Somnolence (3), abdominal distension (4). C: somnolence (4)
Yuan JQ 2013 (146)	Somnolence (NS), dry mouth (NS), poor appetite (NS)
Zhang HB 2011 (159)	I: Somnolence (2), headache (1), nausea (1). C: somnolence (2), headache (2)
Zhang HX 2014 (191)	I: Somnolence (1), diarrhoea (4). C: somnolence (2)
Zhang L 2014 (137)	Somnolence, headache, gastric acid increased, nausea and vomiting (NS)
Zhang Q 2011 (148)	NS
Zhang TL 2011 (158)	None
Zhao HW 2010 (157)	I: Somnolence (4). C: dry mouth (2)
Zhao JH 2010 (156)	I: Somnolence (5). C: dizziness (4)
Zhao YY 2014 (192)	I: Somnolence (2), nausea (1), diarrhoea (3). C: somnolence (4), nausea (3)
Zhao ZY 2004 (152)	NS
Zheng Y 2008 (155)	I: Somnolence (5), gastrointestinal discomfort (3). C: somnolence (4)
Zheng ZY 2014 (193)	I: Somnolence (3), dizziness (2). C: somnolence (2)
Zhong JQ 2011(138)	Gastrointestinal disturbance (NS), drowsiness (NS), paraesthesia (NS), ‘and so on’ (NS)
Zhong X 2005 (153)	NS
Zhou JW 2011 (199)	None
Zhou L 2012 (147)	I: Somnolence and dry month (3). C: somnolence and dry month (2)
Zhu JF 2012 (154)	NS
Zhuang Q 2011 (179)	NS

Notes: C: Control; I: Intervention; NS: not stated

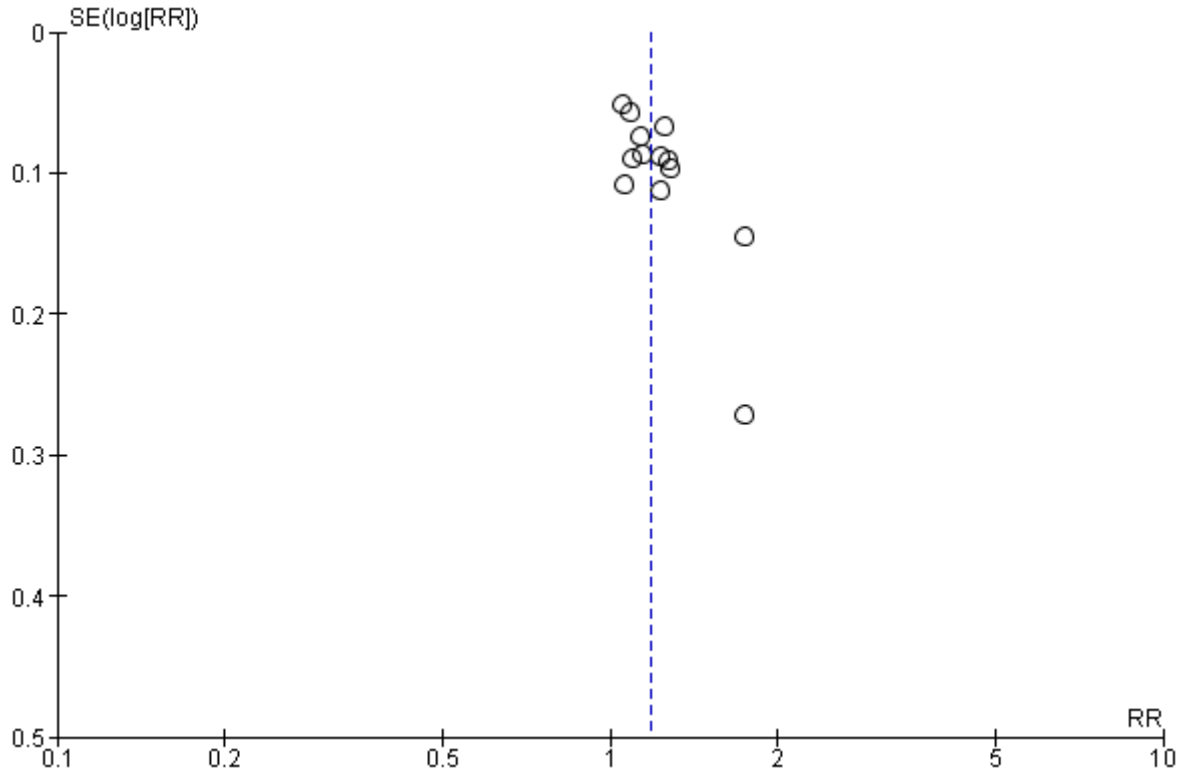

Figure 7.2: Funnel Plot of Chinese Herbal Medicine as Add-on Therapy v. Second-Generation Antihistamines for Chronic Urticaria: ER 30

Notes: CHM: Chinese herbal medicine; ER 30: effective rate based on Chinese Medicine guideline

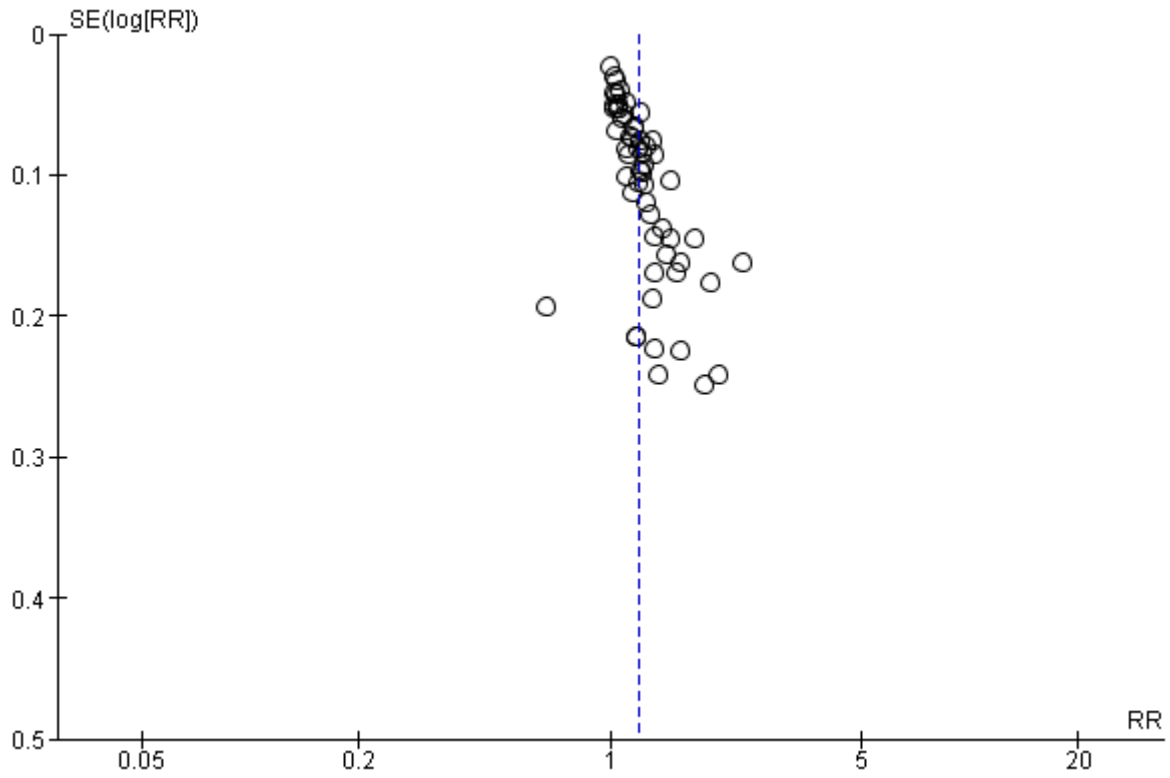

Figure 7.3: Funnel Plot of SSRI 30 (Chinese Herbal Medicine as Add-on Therapy v. Second-Generation Antihistamines for Chronic Urticaria)

Notes: CHM: Chinese herbal medicine; SSRI 30: effective rate based on Symptom Severity Reduction Index

7.4 Discussion

7.4.1 Effects of Interventions

Meta-analysis suggested CHM as add-on therapies to second-generation antihistamines improved the clinical outcomes of patients with chronic urticaria. UAS was used in four studies, but only one study used it as indicated in clinical practice guidelines (10). This single study suggested that CHM as an add-on therapy to antihistamines improved UAS. The usage of UAS in the other three studies differed from prescribed use. Therefore, the clinical relevance is uncertain.

ER 30 and SSRI 30 were the most frequently used outcomes in the included studies. Meta-analysis suggested that CHM as add-on therapy to antihistamines could increase the number of participants who achieved the improvement in symptoms of chronic urticaria by 30% or more. However, substantial statistical heterogeneity was detected for pooled data of both ER 30 and SSRI 30. Sensitivity analysis and subgroup analysis were performed to explore heterogeneity based on sequence generation, treatment duration, comparators and individual CHM formula. The statistical heterogeneity was reduced to an acceptable level for only a few subgroups, such as the individual herbal formula *Yu ping feng san* 玉屏风散 (I^2 = 34%), *Dang gui yin zi* 当归饮子 (I^2 = 0%) and *Xiao feng san* 消风散 (I^2 = 31%). Further, the pooled data from nine studies of *Yu ping feng san* 玉屏风散 indicated a favourable effect of this formula with low levels of statistical heterogeneity, which suggests this formula may be useful for clinical practice. No change or increase in heterogeneity were observed for most subgroups. The reasons for statistical heterogeneity remained unclear, despite subgroup analyses to account for different factors.

7.4.2 Safety

The most commonly reported AEs for participants who received add-on therapies were similar to those experienced by those in the antihistamines group. Somnolence was the most frequently reported AE in both groups. This was surprising because second-generation antihistamines are believed to have fewer sedating effects. Other commonly observed AEs in the CHM as add-on therapy groups were gastrointestinal events. This might be related to CHM and has been found in other health conditions (125). Overall, CHM as an add-on therapy to second-generation antihistamines was well tolerated by patients with chronic urticaria.

7.4.3 How Chinese Herbal Medicine Might Work

Anti-allergy and anti-inflammation are two important pharmacological action mechanisms targeting the pathogenesis of urticaria (10). Six frequently used herbs (*fang feng* 防风, *huang qi* 黄芪, *dang gui* 当归, *gan cao* 甘草, *jing jie* 荆芥 and *bai zhu* 白术) and one formula, *Yu ping feng* 玉屏风散 (*fang feng* 防风, *huang qi* 黄芪 and *bai zhu* 白术), have been shown to have anti-allergic or/and anti-inflammatory actions in experimental studies *in vivo* or *in vitro*.

The ethanol extract of *fang feng* 防风 has been shown to suppress the production of inflammatory mediators, such as NO and prostaglandin E_2 (PGE_2), and pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and IL-6 in lipopolysaccharide (LPS)-induced murine macrophages (RAW 264.7 cells) (207). This cell model is commonly used for the examination of anti-inflammatory activities. The anti-inflammatory action of *fang feng* 防风 extract may result from the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) binding activity and p38 mitogen activated protein kinases (MAPKs) phosphorylation (208, 209), two important transcription factors in the regulation of inflammation. In rats with induced dermatitis, induced ear swelling and ear inflammation were inhibited by oral use of *huang qi* 黄芪 aqueous extract (210). In rats with induced allergic dermatitis, the level of total serum IgE was reduced with topical application of *huang qi* 黄芪 ethanol extract. Additionally, it could suppress the expression of NF-κB (130). The levels of inflammatory mediators (PGE_2, histamine and 5-hydroxytryptamine) were inhibited using *dang gui* 当归 volatile oils in rats with acute inflammation (211). *Gan cao* 甘草 is a key herb used in CM and has been shown to possess both anti-allergic and anti-inflammatory properties (127, 131, 212). Flavonoids from *gan cao* 甘草, such as liquiritigenin, 18β-glycyrrhetinic acid and licochalcone D, potently inhibited the degranulation of RBL-2H3

cells, reducing the release of allergic inflammation mediators such as histamines (131, 212). In ovalbumin-induced mice, the scratching behaviour and IgE production could be also inhibited by liquiritigenin and 18β-glycyrrhetinic acid (131). *Jing jie* 荆芥 and *bai zhu* 白术 have been shown to inhibit allergic reactions in animal models (133, 134, 213). In the plasma of rats with mast cell-mediated immediate-type hypersensitivity, systemic allergic reaction was dose-dependently inhibited by *jing jie* 荆芥 aqueous extract. Further, it significantly reduced histamine levels (133). *Bai zhu* 白术 extract greatly inhibited the oedema in carrageenan-induced rat paw oedema (213).

Yu ping feng san 玉屏风散 and its extracts have been investigated for their anti-allergic and anti-inflammatory effects *in vitro* and *in vivo* (214–216). In mice with Th2 cell-mediated allergic contact dermatitis, ear thickness, ear inflammation and infiltration of inflammation cells were reduced after *Yu ping feng san* 玉屏风散 was administered at 6.5 g/kg (214). This is associated with the reduction of IL-4 levels in the ear tissue, suggesting the anti-allergic and anti-inflammatory effects of *Yu ping feng san* 玉屏风散 may be due to the reduction of IL-4 (214). The expressions of pro-inflammatory cytokines (such as IL-1β, IL-6 and TNF-α) in LPS-induced RAW264.7 cells were suppressed by *Yu ping feng san* 玉屏风散 extract in a dose-dependent mode (215). These anti-inflammatory effects may be due to the suppression of key inflammatory enzymes, namely inducible NO synthase (iNOS) and cyclo-oxygenase-2 (COX-2), partly through NF-κB pathway (216).

7.4.4 Limitations and Implications for Research and Clinical Practice

The most commonly observed outcomes in the included studies were ER 30 and SSRI 30. ER 30 was recommended by CM practice guidelines (63). Despite an extensive search, no reference was found for SSRI 30. While these two outcomes assessed the disease activity of

the two key urticaria symptoms (wheals and pruritus) and reflected the clinical focus, they are not commonly used in international studies. These outcomes were not validated following internationally recognised standards. This limits the findings' translation into clinical practice to some extent. Outcomes recognised internationally should be considered for future clinical trials to evaluate the efficacy of CHM for chronic urticaria.

The recurrence of chronic urticaria symptoms (wheals and pruritus) bothers patients and has significant impact on HR-QoL (10, 14–17). One included study reported DLQI, with some promising results. HR-QoL should be given more focus in future trials. The challenge in the treatment of chronic urticaria is to achieve effective control to prevent recurrence of symptoms. Relapse rate was mentioned in several studies. However, no consensus on the definition of relapse rate was reached. Relapse rate needs to be specified clearly.

7.5 Conclusion

CHM as an add-on therapy to second-generation antihistamines could enhance clinical responses in improving symptoms of chronic urticaria by 30% or more, and appears to be well tolerated by patients. However, the certainty of the findings is limited by factors including the methodological flaws of included studies, substantial statistical heterogeneity and uncertain validity of outcomes.

Chapter 8. Systematic Review 3:

Compound Glycyrrhizin for Psoriasis Vulgaris

8.1 Background

Findings from Chapters 6 and 7 have shown CHM to be effective for chronic urticaria. For psoriasis vulgaris, several SRs have been identified that evaluate the efficacy and safety CHM. Four previous SRs of RCTs (28–31) evaluated topical CHM for psoriasis vulgaris, and one SR (96) evaluated oral CHM. All reviews suggested that CHM was more effective than WM. The limitation of these SRs was the inclusion of some outcomes that are not recognised internationally. The evidence related to QoL was lacking in these SRs. Further, all five SRs provided evidence from a general perspective (overall CHM) and focused on high level evaluation of CHM as an intervention. No reviews that examined the efficacy of a particular herb formula or product were identified.

One CHM product called compound glycyrrhizin (CG), with its key constituent glycyrrhizin extracted from *gan cao* 甘草 , is commonly used in clinical practice in China for both chronic urticaria and psoriasis vulgaris. CG has been evaluated for chronic urticaria and shows promising effects as an add-on therapy to second-generation antihistamines (see Chapter 7). To date, one review was identified that compared CG with acitretin for psoriasis vulgaris (see Section 8.2), but no review of this product has been identified to determine its effectiveness as an add-on therapy to conventional therapy. Therefore, the third SR focused on the add-on effect of CG to conventional therapy for psoriasis vulgaris. This chapter has been published in the journal *Current Medical Research and Opinion* (85).

8.2 Introduction

Psoriasis is a chronic, genetic, systemic and inflammatory disorder, which affects one in 50 people globally (13). Psoriasis vulgaris is the most common type of psoriasis representing approximately 80–90% of psoriasis patients (13). Patients may progress to other types of psoriasis, such as erythrodermic or pustular types, because of inappropriate therapies or infection (12, 13). In addition to disfigured skin lesions that itch, research has linked psoriasis with an increased risk of cardiovascular disease, diabetes and cancer among other morbidities (13).

Guideline-recommended conventional therapy for psoriasis vulgaris includes topical therapies (for example, corticosteroids), phototherapy (NB-UVB) and systemic agents (for example, acitretin) (12, 13). Although these therapies are effective, AEs associated with long-term use remains a major concern for patients (12, 13). There is evidence that the risks of conventional therapies include local and systemic side effects from topical corticosteroids, skin cancer with methoxsalen (psoralen) and ultraviolet A radiation (PUVA) or teratogenicity with systemic retinoids (217, 218). In addition, patients' individual perceptions of disability from psoriasis, and preference for therapies may affect adherence. These factors need be taken into consideration for the treatment of chronic conditions such as psoriasis (217, 218). Up to 50% of patients with skin conditions in the United States (US) and United Kingdom use herbal medicines in conjunction with conventional therapy (24–26).

Gan cao 甘草 (radix *glycyrrhizae* or liquorice root) is a key herb used in CM. Clinically, *gan cao* 甘草 has been used for a range of skin conditions including dermatitis, eczema and psoriasis (219, 220). CG is a manufactured product that contains glycyrrhizin and other ingredients (aminoacetic acid, methionine), with glycyrrhizin (glycyrrhizic acid) as the key component. It is also known as 'Stronger Neo-Minophagen C', and was originally used to

improve liver function abnormalities in chronic liver disease in Japan (221). In recent years, CG has also been used for immunological skin conditions (for example, psoriasis) in China due to its anti-inflammatory activity and immune-modulating effect (222).

A systematic review on concurrent use of CG with acitretin for psoriasis vulgaris concluded that combining CG with acitretin was more effective than using acitretin alone, with fewer AEs (223). This review evaluated the additional benefit and safety of adding CG to all kinds of conventional therapies for psoriasis vulgaris.

8.3 Methods

Five English databases (PubMed, Embase, CINAHL, CENTRAL and AMED), one Japanese database (CiNii) and four Chinese databases (CBM, CNKI, CQVIP and Wanfang Data) were searched from inceptions to July 2015. Search terms were grouped according to intervention (glycyrrhizin and variants), condition (psoriasis and variants), and study design (randomly, randomised and variants), with adjustments for each database. Identified citations were exported to Endnote reference management software for further screening.

RCTs comparing CG plus guideline-recommended conventional therapy with the same conventional therapy alone for psoriasis vulgaris were included (12, 13). The primary outcome was the proportion of patients achieving PASI 60 (that is, 60% or greater reduction in PASI score). PASI 60 is recommended in *Consensus of diagnosis and treatment of psoriasis vulgaris in integrative medicine* published in China (94). PASI 50/70 are considered treatment goals based on international guidelines (12, 95). As suggested in previous SRs (28, 96), PASI 60 was frequently used in RCTs in China as the primary outcome. Secondary outcomes included PASI 90 (clinically cured), measures of HR-QoL (such as DLQI), relapse rate and AEs.

Data were extracted independently by two reviewers (Jingjie Yu and Claire Zhang). These reviewers evaluated methodological quality using the risk of bias tool developed by the Cochrane Collaboration (89). Disagreement was resolved through discussion or consultation with a third reviewer (Meaghan Coyle).

Outcome data were analysed using Review Manager 5.3 software (97). Dichotomous data were expressed as RR and continuous data expressed as MD, with 95% CI. RD was presented as the actual difference in risk between the intervention and control groups. Fixed effects analysis was used. Statistical heterogeneity was evaluated using the I^2 statistic. Subgroup analysis was planned according to conventional therapy type and preparation type of CG, while publication bias was assessed by visual inspection of funnel plots. This review protocol was registered in PROSPERO (CRD42015027763).

8.4 Results

Electronic database searches retrieved 724 potentially relevant citations. After removal of duplicates, 444 records were screened. Through title and abstract screening, 413 records did not meet the inclusion criteria. Exclusions included studies of conditions other than psoriasis vulgaris, non-RCTs and irrelevant outcomes. Further review of full text was required for 31 articles, and 11 RCTs met the inclusion criteria (see Figure 8.1). All trials were conducted in China and published in Chinese language journals between 2006 and 2014. A two-arm parallel design was applied for all included studies except one, which used a three-arm design (224). The sample size of the largest study was 200 (225) and the smallest was 66 (226) (see Table 8.1).

In total, 1,200 patients with psoriasis vulgaris completed these trials in hospital outpatient or inpatient departments. Seven studies (224–230) stated the disease stages of participants,

including progressive and stationary stages. The severity of psoriasis vulgaris was mentioned as mild to severe in three studies (225–227). Participants suffered from psoriasis vulgaris from one month (224) to 39 years (230). The mean age of participants ranged from 30.5 (231) to 40.3 years (232). Participants received treatment for four (224, 227, 230, 233) or eight weeks (225, 226, 228, 229, 232), with one study providing treatment for up to 12 weeks (234). Follow-up after two months was conducted in one study (231).

8.4.1 Intervention and Co-intervention/Comparator

The intervention group used CG and specific conventional therapy, while the comparison group used corresponding conventional therapy alone (see Table 8.2). CG was administered orally or intravenously. Capsules or tablets were given orally three times per day in seven studies (226, 229-234), with the dosage being prescribed as 50 or 75 mg in four studies (229, 231, 232, 234). The remaining three studies described administration of CG as two or three capsules/tablets each time (226, 230, 233). Infusion was used with 40–60 ml or 80 mg of CG in four studies (224, 225, 227, 228). All studies administered CG within the suggested daily dosage (235, 236).

Five studies used CG (Stronger Neo-Minophagen C) imported from Japan (225, 228, 230, 232, 234), while two studies used CG products manufactured in China with the same chemical composition (229, 233). No information relating to the manufacturing source of CG was mentioned in the remaining studies. Conventional therapy included topical corticosteroids (230, 231, 233), NB-UVB (224, 227, 232), acitretin (225, 226, 234) and a combination of the above agents (228, 229). Dosing scheme of conventional therapy was consistent with guidelines (12, 13).

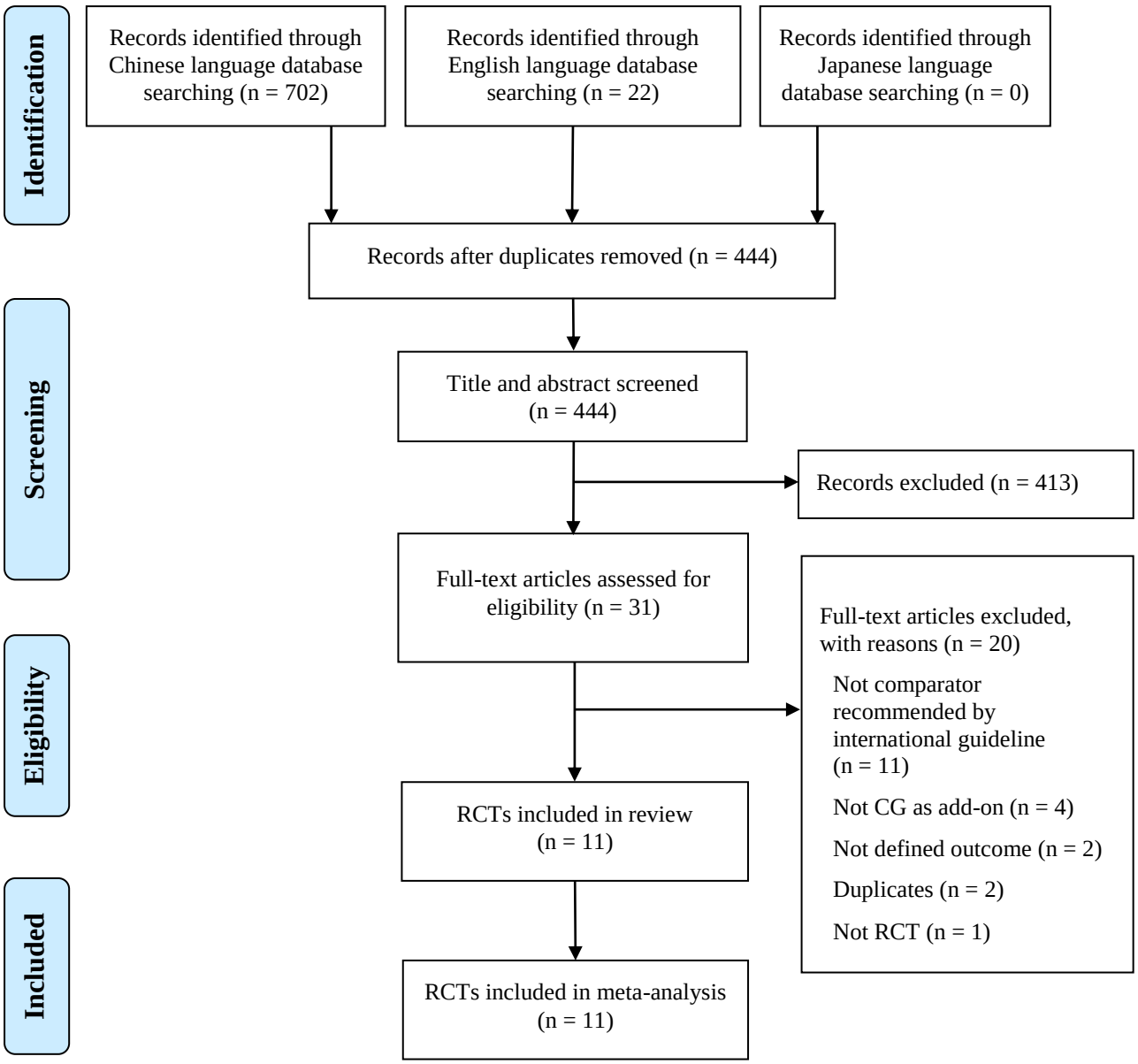

Figure 8.1: PRISMA Flow Chart of Study Selection Process: Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris

Notes: CG: Compound Glycyrrhizin; RCT: randomised controlled trial

Table 8.1: Characteristics of Included Randomised Controlled Trials: Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris

First author, publication year	Country; setting	Blinding; number of arms	Treatment duration; follow-up duration	Stage; severity	Duration of psoriasis	No. of participants randomised/ assessed; dropouts	Age: mean (SD) (or range); gender M/F	Intervention	Control
Du, 2014 (229)	China; hospital outpatients	NS; 2	8 w; 0	I: PS and SS; NS	17.5 (4.13) y	I: 60/60; 0	I: 31.24 (9.45); 39/21	CG, acitretin, NB-UVB	Acitretin, NB-UVB
				C: PS and SS; NS	18.4 (4.4) y	C: 58/58; 0	C: 32.93 (11.72); 37/21		
Huang, 2014 (228)	China; hospital patients (NS)	NS; 2	8 w; 0	I: PS; NS	8.6 (1.8) y	I: 45/45; 0	I: 43.5 (3.6); 25/20	CG, mometasone furoate cream, 0.1 % tretinoin cream, NB-UVB	Mometasone furoate cream, 0.1 % tretinoin cream, NB-UVB
				C: PS; NS	8.2 (2.3) y	C: 45/45; 0	C: 45.3 (5.8); 23/22		
Jiang, 2014 (226)	China; hospital out/inpatients	NS; 2	8 w; 0	I: PS; psoriasis lesion area ≥ 40 % BSA	6.5 y	I: 34/34; 0	I: 33.5; 18/16	CG, acitretin	Acitretin
				C: PS; psoriasis lesion area ≥ 40 % BSA	5.7 y	C: 32/32; 0	C: 37.5; 17/15		

First author, publication year	Country; setting	Blinding; number of arms	Treatment duration; follow-up duration	Stage; severity	Duration of psoriasis	No. of participants randomised/ assessed; dropouts	Age: mean (SD) (or range); gender M/F	Intervention	Control
Luo, 2006 (232)	China, outpatients	NS; 2	8 w; 0	I: NS; NS	1.47 y	I: 51/51; 0	I: 38.15 (20-61); 27/24	CG, NB-UVB, moisture cream	NB-UVB, moisture cream
				C: NS; NS	1.31 y	C: 46/46; 3	C: 40.22 (19-63); 24/22		
Liu, 2008 (225)	China; hospital patients (NS)	NS; 2	8 w; 0	I: NS; psoriasis lesion area ≤ 30 % BSA	3.36 (5.72) y	I: 100/100; 0	I: 37.00 (10.50); 71/29	CG, acitretin	Acitretin
				C: NS; psoriasis lesion area ≤ 30 % BSA	3.42 (5.46) y	C: 100/100; 0	C: 37.50 (10.25); 70/30		
Ma, 2011 (231)	China; hospital out/inpatients	NS; 2	4 w; 2 m	NS; NS	6.7 y (2 m–30 y)	I: 47/47; 0	Total: 30.5 (19-66); 46/44	CG, mometasone furoate cream	mometasone furoate cream
						C: 43/43; 0			
Wu, 2010 (224)	China; hospital inpatients	NS; 3	4 w; 0	Total: PS and SS; NS	8.7 y (1 m–20 y)	I: 42/42; 0	Total: 32.6 (21-59); 66/54	CG, NB-UVB	C1: NB-UVB C2: CG
						C1: 40/40; 0			
						C2: 38/38; 0			

First author, publication year	Country; setting	Blinding; number of arms	Treatment duration; follow-up duration	Stage; severity	Duration of psoriasis	No. of participants randomised/ assessed; dropouts	Age: mean (SD) (or range); gender M/F	Intervention	Control
Wang, 2014 (233)	China; hospital outpatients	NS; 2	4 w; 0	I: NS; NS	5.8 (1.2) y	I: 60/60; 0	I: 37.4 (2.9); 39/21	CG, desonide cream	desonide cream
				C: NS; NS	5.6 (1.5) y	C: 60/60; 0	C: 38.6 (3.1); 31/29		
Yao, 2010 (230)	China; hospital patients (NS)	NS; 2	4 w; 0	Total: PS and SS; NS	1–39 y	I: 48/48; 0	I: 42.3; 27/21	CG, compound flumetasone ointment	compound flumetasone ointment
						C: 44/44; 0	C: 38.9; 25/19		
Yang, 2014 (227)	China; hospital outpatients /inpatients	NS; 2	4 w; 0	I: PS and SS; PASI ≥ 10	6.4 (2.5) y	I: 65/65; 0	I: 37.4(6.1); 35/30	CG, NB-UVB	NB-UVB
				C: PS and SS; PAS I≥ 10	6.2 (2.4) y	C: 60/60; 0	C: 35.5 (6.4); 32/28		
Zhang, 2014 (234)	China; hospital patients (NS)	NS; 2	8–12 w; 0	I: NS; NS	6.3 (5.0) y	I: 60/60; 0	I: 37.1 (9.6); 37/23	CG, acitretin	Acitretin
				C: NS; NS	5.7 (4.2) y	C: 60/60; 0	C: 35.6 (8.9); 35/25		

CG: Compound Glycyrrhizin; C: Control; I: Intervention; m: months; NB-UVB: narrow-band UVB; NS: not stated; PASI: Psoriasis Area and Severity Index; PS: progressive stage; SS: stationary stage; w: weeks, y: years

Table 8.2: Intervention/Comparators of Included Randomised Controlled Trials: Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris

First author, publication year	Compound glycyrrhizin preparation type and dosage	Country of compound glycyrrhizin manufacture	Conventional therapy	Dosage and administration
Du, 2014 (229)	Capsule, 50 mg po tid	China	NB-UVB; Acitretin	NB-UVB, qod; acitretin, 10 mg po bid
Huang, 2014 (228)	Injection, 60–80 ml ivgtt qd for 10 days consecutively, intermittent for four days	Japan	Mometasone furoate cream; 0.1 % tretinoin cream; NB-UVB	Mometasone furoate cream, topical use; 0.1 % tretinoin cream, 30–50 mg topical use, qn; NB-UVB, twice a week
Jiang, 2014 (226)	Capsule, two capsules po tid	NS	Acitretin	0.4–0.7 mg/kg·d as initial oral dosage, adjusted dosage based on condition severity and medication tolerance, 10–20 mg qd as maintenance dosage
Luo, 2006 (232)	Tablet, 75 mg po tid	Japan	NB-UVB	NB-UVB, thrice a week
Liu, 2008 (225)	Injection, 60 ml ivgtt qd for 20 days consecutively	Japan	Acitretin	30 mg po qd for 45 days consecutively, 20 mg po qd as rest dosage
Ma, 2011 (231)	Tablet, 50 mg po tid	NS	Mometasone furoate cream	Topical use, qd
Wu, 2010 (224)	Injection, 40 ml ivgtt qd for 10 days	NS	NB-UVB	NB-UVB, qod, 10 sessions in total
Wang, 2014 (233)	Capsule, three capsules po tid	China	Desonide cream	Topical use, tid
Yao, 2010 (230)	Tablet, three tablets po tid	Japan	Compound flumetasone ointment	Topical use, bid
Yang, 2014 (227)	Injection, 80 mg ivgtt qd	NS	NB-UVB	Twice a week
Zhang, 2014 (234)	Tablet, 75 mg po tid	Japan	Acitretin	20–40 mg/d as initial oral dosage, adjusted dosage based on condition severity and medication tolerance, 10–20 mg qd as maintenance dosage

Notes: bid: twice daily; ivgtt: intravenously guttae; mg: milligram; ml: milliliter; NB-UVB: narrow-band UVB; NS: not stated; po: administrated orally; qd: once daily; qod: every other day; tid: three times daily

8.4.2 Outcome Measures

Clinical response was evaluated by PASI 60 in all studies and all but one used PASI 90 (228). Relapse rate was reported in one study (231). However, the definition of relapse rate was not specified. None of the included studies reported DLQI. All but one study (228) reported AEs.

8.4.3 Risk of Bias Assessment

Four studies used random number tables to allocate participants and were judged as low risk for sequence generation (227, 229, 233, 234). One study was assessed as high risk because participants were assigned to different groups based on visiting order (231). No clear description of sequence generation was provided in the remaining six studies. Therefore, they were deemed an unclear risk. All studies were assessed as posing an unclear risk for allocation concealment due to a lack of detailed information. Blinding was not applied to participants or personnel in any of the included studies. Therefore, all studies were judged as high risk for this domain. Blinding of outcome assessors was not mentioned for the included studies and all were assessed as unclear risk. Dropouts related to AEs caused by NB-UVB were reported in one study (232), and the number was balanced between the two groups. Hence, it is unlikely to cause bias. No dropouts were reported for the remaining studies. Consequently, all studies were judged as low risk for incomplete outcome data. None of the studies reported details of trial registration or had published protocols, and all were assessed as unclear risk for selective outcome reporting (see Figure 8.2).

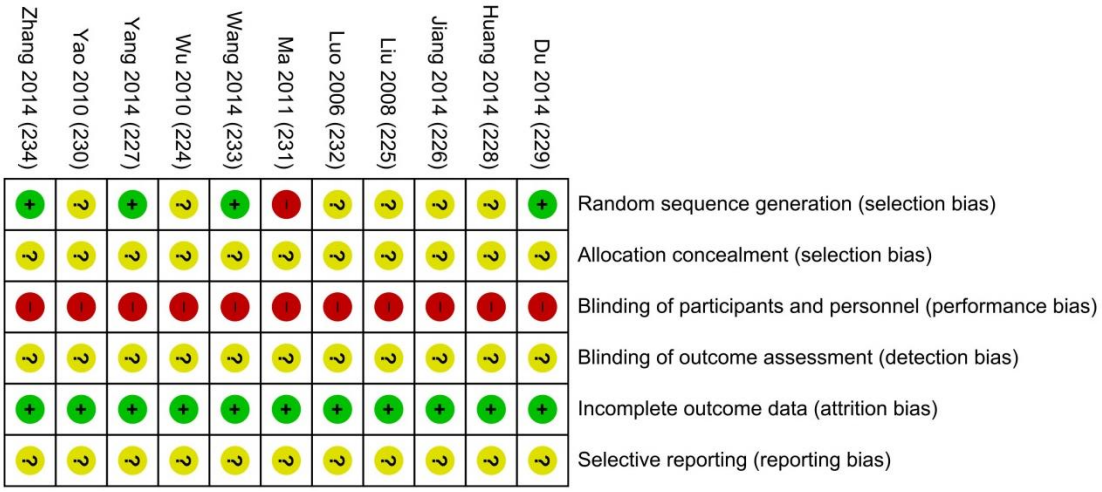

Figure 8.2: Risk of Bias Assessment: Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris

8.4.4 Effects of the Intervention

Add-on Effect of CG to Conventional Therapy

Meta-analysis showed that the chance of achieving PASI 60 (RR: 1.30 [1.21, 1.40], I^2 = 6%, RD: 19%) or PASI 90 (RR: 1.37 [1.21, 1.56], I^2 = 0%, RD: 14%) was higher in those who received CG plus conventional therapy than in those who received conventional therapy alone. Statistical heterogeneity was low.

Subgroup Analysis by Therapy Type

Pooled data from three studies (230, 231, 233) showed significant improvement in the number of people achieving PASI 60 (RR: 1.46 [1.23, 1.74], I^2 = 0%, RD: 24%) and PASI 90 (RR: 1.44 [1.07, 1.94], I^2 = 0%, RD: 14%), when CG was used as an add-on therapy to topical corticosteroids. In addition, the combination therapy reduced the relapse rate in one study (RR: 0.34 [0.21, 0.54], RD: -68%) (231) (see Figure 8.3).

Compared to NB-UVB alone, the combination of CG and NB-UVB was more likely to increase the number of people achieving PASI 60 (RR: 1.19 [1.07, 1.33], I^2 = 0%, RD: 14%) in three studies (224, 227, 232). A significant difference was also found for PASI 90 (RR: 1.41 [1.16, 1.73], I^2 = 53%, RD: 18%), but with moderate statistical heterogeneity. Additional subgroup analysis, including two studies (224, 227) with the same treatment duration, reduced the heterogeneity (RR: 1.28 [1.05, 1.56], I^2 = 0%, RD: 16%).

Meta-analysis including three studies (225, 226, 234) suggested that CG plus acitretin was superior to acitretin alone in terms of PASI 60 (RR: 1.30 [1.15, 1.47], I^2 = 0%, RD: 19%) and PASI 90 (RR: 1.30 [1.01, 1.68], I^2 = 0%, RD: 10%) (see Figure 8.3).

Subgroup Analysis by CG Preparation Type

As an add-on therapy to NB-UVB, the treatment effect of oral CG was not different to infusion in terms of PASI 60 (test for subgroup differences: Chi^2 = 0.91, df = 1 [P = 0.34], I^2= 0%), or PASI 90 (test for subgroup differences: Chi^2 = 2.54, df = 1 [P = 0.11], I^2 = 60.6%). Similarly, no difference was found for PASI 60 (test for subgroup differences: Chi^2 = 0.09, df = 1 [P = 0.76], I^2 = 0%) or PASI 90 (test for subgroup differences: Chi^2 = 0.01, df = 1 [P = 0.94], I^2 = 0%) between oral use and infusion of CG as add-on therapy to acitretin (see Table 8.3).

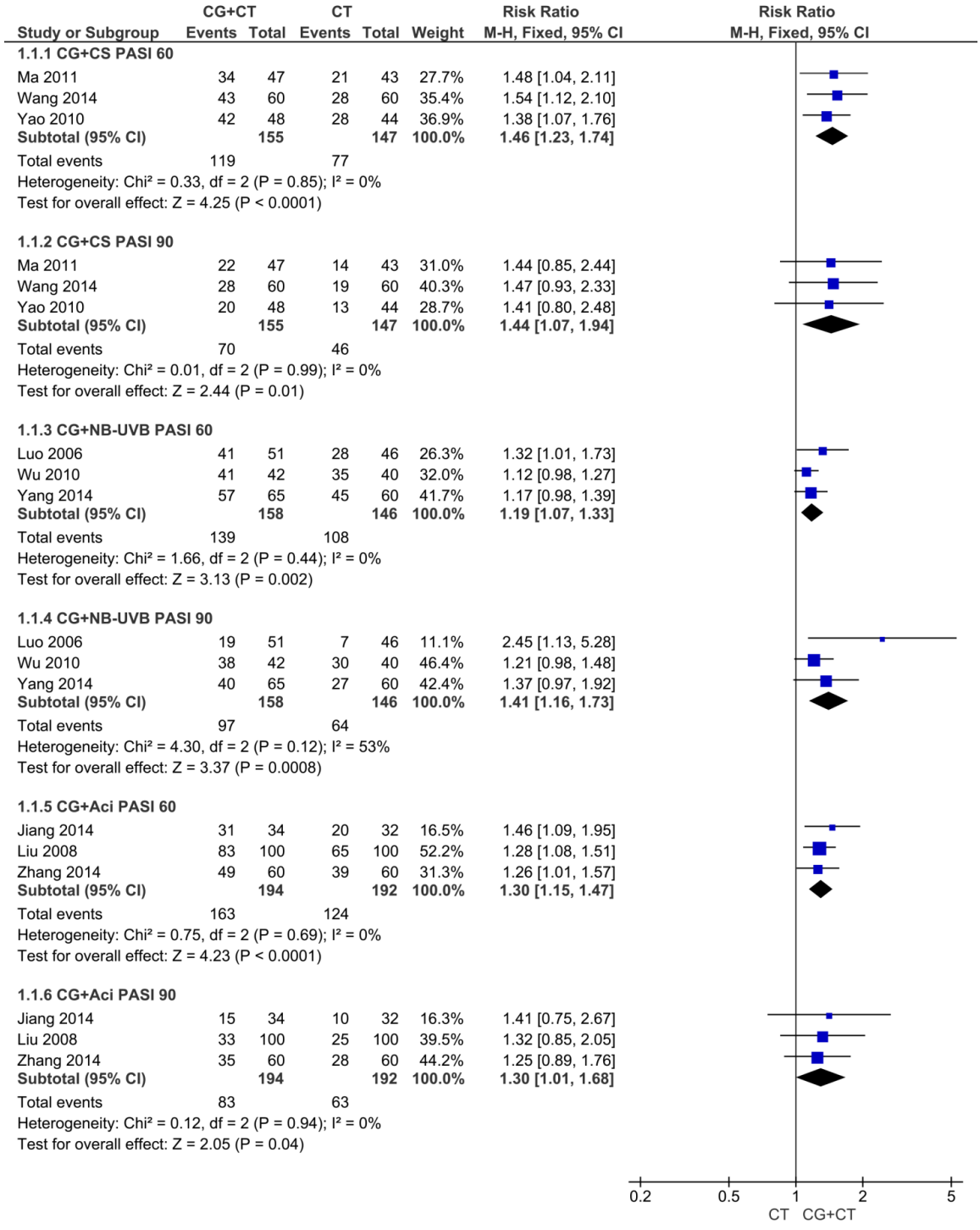

Figure 8.3: Forest Plot of Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris: PASI 60 and PASI 90

Notes: Aci: acitretin; CG: Compound Glycyrrhizin; CS: topical corticosteroid; CT: conventional therapy; NB-UVB: narrow-band UVB; PASI 60: 60% or greater reduction of PASI score; PASI 90: 90% or greater reduction of PASI score

Table 8.3: Effect Size Analysis: Subgroup Analysis According to Preparation Type of Compound Glycyrrhizin

Comparison	Outcome measures	Preparation type	Number of studies (studies: first author, year)	Number of participants analysed	Effect estimate (RR, 95 % CI, 95 % CI, I^2; RD %)
CG plus NB-UVB v. NB-UVB	PASI 60	Tablet	1 study (Luo 2006 [232])	97	RR: 1.32 [1.01, 1.73]*; NA; 20 %
		Injection	2 studies (Wu 2010, Yang 2014 [224, 227])	207	RR: 1.15 [1.02, 1.28]*, I^2=0%; 12 %
		Test for subgroup differences: Chi^2 = 0.91, df = 1 (P = 0.34), I^2 = 0%			
	PASI 90	Tablet	1 study (Luo 2006 [232])	97	RR: 2.45 [1.13, 5.28]*; NA; 22 %
		Injection	2 studies (Wu 2010, Yang 2014 [224, 227])	207	RR: 1.28 [1.05, 1.56]*, I^2=0%; 16 %
		Test for subgroup differences: Chi^2 = 2.54, df = 1 (P = 0.11), I^2 = 60.6 %			
CG plus acitretin v. acitretin	PASI 60	Tablet/capsule	Two studies (Jiang 2014, Zhang 2014 [226, 234])	186	RR: 1.33 [1.11, 1.58]*, I^2=0%; 21%
		Injection	One study (Liu 2008 [225])	200	RR: 1.28 [1.08, 1.51]*; NA; 18%
		Test for subgroup differences: Chi^2=0.09, df = 1 (P = 0.76), I^2 = 0%			
	PASI 90	Tablet/capsule	Two studies (Jiang 2014, Zhang 2014 [226, 234])	186	RR: 1.29 [0.95, 1.76], I^2 = 0 %; 12 %
		Injection	One study (Liu 2008 [225])	200	RR: 1.32 [0.85, 2.05]; NA; 8 %
		Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.94), I^2 = 0 %			

Note: CI: confidence interval; NA: not applicable; NB-UVB: narrow-band UVB; PASI: Psoriasis Area and Severity Index; RD: risk difference; RR: risk ratio; *: significantly different

8.4.5 Adverse Events

All but one study (228) reported AEs. The reported number of AEs was similar in the intervention and control groups (101 v. 102, respectively) (see Table 8.4). Five of the included studies reported that AEs were related to CG (224, 226, 229, 230, 232). Among them, two studies suggested that the addition of CG could reduce AEs caused by acitretin or NB-UVB (226, 232); another three studies (224, 229, 230) found CG might increase blood pressure (two cases) and cause oedema (seven cases), such as bimalleolar oedema, or oedema on the dorsum of feet and eyelids. The remaining AEs were consistent with the safety profile of conventional therapy.

8.4.6 Publication Bias

The risk of publication bias appeared to be low as illustrated in the symmetrical appearance of the funnel plot for PASI 60 (11 studies) (see Figure 8.4).

Table 8.4: Adverse Events of Included Randomised Controlled Trials: Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris

Study	Adverse events	Authors' conclusion
Du, 2014 (229)	I: dry skin and eyes (3), mild increase in blood pressure (2)	Compound glycyrrhizin may cause increase of blood pressure, but protect liver function. Other AEs were caused by conventional therapies
	C: mild red skin and itch (4), mild increase of ALT and AST (2)	
Huang, 2014 (228)	NS	NS
Jiang, 2014 (226)	I: dry skin, mouth and lips (22), high aminotransferase (1), hyperlipidaemia (2)	Adding compound glycyrrhizin could reduce the AEs of liver caused by acitretin
	C: dry skin, mouth and lips (30), high aminotransferase (3), hyperlipidaemia (4)	
Liu, 2008 (225)	I: dry mouth (26), skin itch (4), abnormal liver function (1), gastrointestinal reaction (5)	No additional AE was caused by compound glycyrrhizin
	C: dry mouth (21), skin itch (3), abnormal liver function (1), gastrointestinal reaction (4)	
Luo, 2006 (232)	I: mild redness (3)	Adding compound glycyrrhizin could reduce the AEs caused by NB-UVB
	C: redness (eight in total, three were severe)	
Ma, 2011 (231)	I: skin redness and itch (3)	Mild AEs were caused by the pharmacotherapy drugs
	C: skin redness and itch (4)	
Wang, 2014 (233)	I: dry skin (1)	Both treatments are safe for psoriasis vulgaris
	C: red skin (1)	
Wu, 2010 (224)	I: skin pigmentation and dryness for all cases, skin itch (5), red skin (3), skin redness and burning sensation (2), bimalleolar oedema (1), oedema on the dorsum of feet and eyelid (1)	Both treatments are safe for psoriasis vulgaris
	C1: skin pigmentation and dryness for all cases, skin itch (6), red skin (4)	
	C2: skin itch exacerbation (1), bimalleolar oedema and oedema on the dorsum of feet (1)	
Yang, 2014 (227)	I: red skin and burning sensation (7)	Both treatments are safe for psoriasis vulgaris
	C: none	

Study	Adverse events	Authors' conclusion
Yao, 2010 (230)	I: red and itchy skin (4), oedema (5) C: red and itchy skin (5)	Both treatments are safe for psoriasis vulgaris
Zhang, 2014 (234)	Dry skin and lips, scale and red skin, itch skin (NS)	Both treatments are safe for psoriasis vulgaris

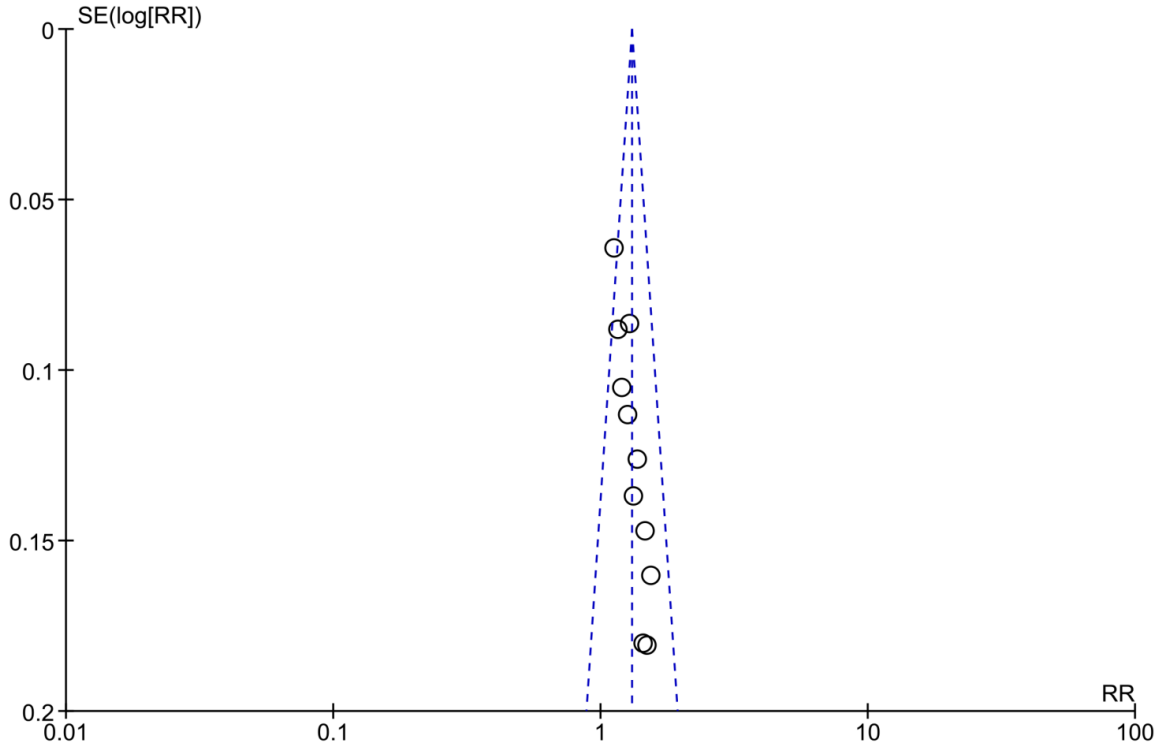

Figure 8.4: Funnel Plot of Compound Glycyrrhizin as Add-on Therapy v. Conventional Therapy for Psoriasis Vulgaris: PASI 60

Notes: PASI 60: 60% or greater reduction of PASI score

8.5 Discussion

Meta-analysis indicated that the addition of CG significantly increased the number of patients achieving PASI 60 by 19% and PASI 90 by 14% when compared with conventional therapy alone. Specifically, the add-on effect of CG was shown when used as an adjunct therapy to topical corticosteroids, NB-UVB and acitretin. The addition of CG to topical corticosteroids increased the number of patients achieving PASI 60 by 24% compared with topical corticosteroid alone. The findings from this review suggest that a combination of CG and topical corticosteroids enhances clinical response greatly. As add-on therapy to acitretin, CG also increased the chance of achieving PASI 60 and PASI 90, confirming findings previously

reported (223). In addition, the treatment effect of CG did not differ when used orally or intravenously. The administration of CG is flexible and convenient in clinical practice.

The finding of low statistical heterogeneity in several meta-analyses was surprising. This may be due in part to the use of a standardised manufactured product CG with similar duration (four or eight weeks), and dosing regimen for conventional therapy in line with clinical practice guidelines. There were insufficient data to confirm the long-term add-on effect of CG to conventional therapies. Adding CG to conventional therapies could increase efficacy of treatment and shorten the treatment duration required. This would reduce the risk of side effects from long-term use of conventional therapies.

Gan cao 甘草 extracts, in particular glycyrrhizin and its derivatives, have proven benefits for skin disorders in experimental studies. Glycyrrhetinic acid inhibits the oedema response to capsaicin in mice ears by preventing vascular permeability induced by vasoactive agents (237); glycyrrhizin treatment reduced the number of human melanoma cells after UVB irradiation (238). Further, the ammonium salt of glycyrrhizin has anti-inflammatory properties (239) and glycyrrhizin prevented ICAM-1 expression through inhibition of the ERK/p38 MAPK and NF-κB signaling pathways in keratinocytes (222).

In addition, two per cent topical preparation of glycyrrhetinic acid is a potent inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase (11β -OHSD), which is present in diseased skin such as psoriasis and eczema (240). In the presence of glycyrrhetinic acid, the anti-inflammatory activity of hydrocortisone could be greatly enhanced, which is beneficial for inflammatory cutaneous disorders (240). Consistently, the findings of this review also indicate that adding CG could greatly enhance the efficacy of corticosteroids.

AEs reported in included trials suggest that CG may increase blood pressure and cause oedema. Hypokalemia and/or hypertension have been reported with intravenous use of CG for hepatitis (241). Allergic reactions, including hives and anaphylaxis, were identified in a review of adverse drug reactions (ADR) to CG injection in China (242). Variation in ingredients and impurities in CG injections have been reported among manufacturers (243), which may be potential source of ADR (244). Patients with cardiovascular disease or hypertension who are receiving CG should be monitored, and greater caution should be used for intravenous use of CG than for than oral administration.

8.5.1 Limitations

The included studies were methodologically flawed. Potential bias may be caused by unclear methods of randomisation, lack of blinding and selective outcome reporting. Adequately powered, appropriately randomised, double-blinded, placebo-controlled trials with sufficient reporting are warranted.

HR-QoL was not assessed in any study. Although psoriasis is not a life-threatening condition, it impedes sufferers' QoL. Further studies should incorporate assessments of patients' clinical symptoms and QoL. One study (231) reported relapse rates without describing the criteria used. Recurrence is an ongoing issue for patients and dermatologists and can be difficult to manage clinically. Follow-up should be included in further studies to monitor the long-term effects of CG.

The additional benefit of adding CG to conventional therapy has been demonstrated in this review. However, the combination of therapies that could achieve greater clinical response remains uncertain. Three studies reported severity of participants' disease but were unable to perform subgroup analysis. The sample size in subgroup analyses was relatively small, which may overestimate the true effects (89). Network meta-analysis or clinical trials with adequate

sample sizes are needed to determine which combinations of CG and conventional therapy can provide the most efficacious treatment option for psoriasis vulgaris.

ADR/AE of CG described in the literature (245) have not been documented in the report of the National Centre for ADR monitoring in China. As little information was provided in the included studies, and due to a lack of standard reporting items for ADR and AE (245, 246), the safety profile of CG is incomplete. Issues common to herb injection more broadly include overdose, menstruum, drop speed of infusion and drug incompatibility, which may cause ADR or AE (245, 246).

8.6 Conclusion

CG plus conventional therapy appears to provide enhanced clinical response using PASI 60 and 90 as measurements. Further, it does not increase the frequency of AEs for patients with psoriasis vulgaris. However, the findings should be interpreted with caution due to the significant methodological limitations of included studies. The long-term add-on effect is uncertain. Studies that are more robust are required to evaluate CG to confirm these benefits.

Chapter 9. Patient Experiences of Using Chinese Herbal Medicine for Chronic Skin Conditions: A Qualitative Study

9.1 Introduction

Interest in CAM is increasing (247, 248). Many studies have examined the use and prevalence of CAM in a variety of patient groups and settings (247, 249, 250), including people with skin conditions (24, 25, 251). Most of these studies report quantitative data, with relatively few studies exploring patients' experiences of using CAM.

Data from the National Health Interview Survey in the US showed CAM use to be high in people with skin conditions (84.5%), although a small minority (1.1%) used CAM to treat the skin condition (25). In a survey on CAM use in people attending a contact dermatitis clinic, CAM was used to treat the skin condition in 30% of participants, with CHM accounting for 18% of CAM use (251). The survey identified higher CAM use among Indo-Asian patients. Participants based their decision to use CAM on recommendations from friends and family members with skin disease, advice from an orthodox health care professional, or media (print or digital).

As one of the popular forms of CAM, CHM has been increasingly evaluated in term of its efficacy and safety in randomised trials. However, there is a lack of information about the experiences of people who use CHM to treat chronic skin conditions (the end user's perspective). To address this gap, the researcher conducted in-depth interviews with people who have used CHM for two common chronic skin conditions: chronic urticaria and psoriasis vulgaris. This provided important evidence for translating the clinical evidence (see Chapters 6–8) into effective CM clinical practice.

9.2 Aim

The purpose of this study was to explore people's realities of living with a chronic skin condition, either chronic urticaria or psoriasis vulgaris, and their experiences using CHM to manage the condition. This project examined the impact of the conditions on their health and everyday lives (for example, time for management, financial cost and social impact), the factors that motivate people to seek out CHM for these skin conditions and the experiences of using CHM for chronic skin conditions.

9.3 Significance of the Study

Use of CAM is increasing, with many people opting to treat skin conditions with CAM (including CHM). While clinical trials and SRs evaluate the efficacy and safety of CHM for skin conditions, there is little information on the motivators that lead people to choose CHM to manage their skin condition and their experiences with CHM. Through semi-structured interviews with people living with either chronic urticaria or psoriasis vulgaris, the findings of this project provided valuable information that may inform clinical decision-making and guide future research of CHM use for dermatological conditions.

9.4 Study Design

The method for this study is qualitative description. Qualitative description seeks to provide a 'rich description of the experience/event/process depicted in easily understood language' (252). This project explored the experiences of people with chronic skin conditions in terms of the impact of the condition on their health and life, and their experiences in using CHM. Therefore, it is highly suited to qualitative descriptive methods. Individual, in-depth interviews were conducted with people who have used CHM to manage psoriasis vulgaris or chronic urticaria.

9.5 Method

Data were collected via semi-structured interviews. An interview guide was developed (see Appendix 4) that guided the interview and was reviewed throughout the project as new themes emerged. No additional changes were required.

9.5.1 Sample Selection

The sample for the study was drawn from people who have consulted a CM practitioner for treatment of chronic urticaria (defined as urticaria present on most days for six weeks or more) or psoriasis vulgaris, and who have received CHM in Australia or China within the last five years. Participants were aged between 18 and 80 years and able to read and speak English or Chinese. Written informed consent was obtained prior to interview (see Appendix 5), including consent to audio recording. People with conditions other than chronic urticaria or psoriasis vulgaris, or using CM therapy other than CHM, or with severe health conditions such as cardiovascular or renal dysfunction were excluded.

9.5.2 Sample Size

It was anticipated that approximately 20 participants in Australia and 20 participants in China would be recruited to the study. Gender balance was not required. The final number was determined by theoretical or population saturation (253).

9.5.3 Participant Recruitment

In Australia, recruitment adopted several strategies:

1. Advertisements were placed in the waiting rooms of local CM practitioners' clinics and the RMIT University Health Sciences Clinic (see Appendix 6).

2. Information about the study was provided to new and existing CM patients who presented to the RMIT University Health Sciences Clinic.
3. The study was promoted through support groups for people with psoriasis vulgaris and chronic urticaria after obtaining permission from support group moderators.

In China, potential participants were identified by dermatologists on attendance at the Department of Dermatology in Guangdong Provincial Hospital of Chinese Medicine. Additionally, poster advertisements were placed in the department waiting room. Potentially eligible participants were approached directly by research personnel when they visited the Department of Dermatology of this hospital to discuss the details of the study and to invite them to participate.

9.5.4 Data Collection

Eligible participants were provided with written information about the research study, and any questions were answered by research personnel. If the person was eligible and agreed to participate, an interview time was arranged and written informed consent was obtained. Interviews were conducted in both Australia and China. For participants located in the Melbourne metropolitan area, interviews were conducted either at RMIT or at the participants' home if more convenient. In China, interviews were conducted at Guangdong Provincial Hospital of Chinese Medicine, Guangzhou.

Each interview took approximately 30–60 minutes. Interviews were semi-structured and followed an interview guide (see Appendix 4), which covered experiences with the condition in terms of impact on health and daily life, reasons for choosing CHM, and experiences with using CHM for the condition.

An audio recording of the interview was made and for interviews conducted in English, a second researcher was present to record additional non-verbal details of the interview. This was not possible for interviews conducted in China, so the interviewer recorded non-verbal details while conducting the interview. Interviews were conducted in English or Chinese (Mandarin) depending on the participant's preference.

The content to be covered in the interview was unlikely to raise concerns for participants or researchers. Regardless, participants were advised at the time of obtaining informed consent that any information they provided would remain confidential, and that audio-files and transcripts would be de-identified and stored in a locked filing cabinet or in a password-protected computer.

Participants were advised that they could decline to respond to any question they did not wish to answer. The researcher observed the verbal and non-verbal responses of the participant throughout the interview. If the participant looked uncomfortable or expressed concerns with the question or line of questioning, they were asked if they would prefer not to answer that question, and whether they wished to proceed with the interview. The participants were advised that if they were upset, they could discuss the issues further with one of the study investigators (Tony Zhang). If they wanted to lodge a complaint, the contact details of ethics committee from RMIT and the Guangdong Provincial Hospital of Chinese Medicine were provided on the Patient Informed Consent Form (PICF) (see Appendix 5).

9.5.5 Data Analysis

Thematic content analysis was used to explore the data. Interviews were transcribed in full and verbatim in the original language. Transcripts were de-identified and uploaded to QSR NVivo 11 software (QSR International) for data management and coding. Transcripts were coded line by line using 'open coding' to label common themes. Participants' identifiable

information was replaced with pseudonyms. This data management and coding process involved several steps:

- Read and re-read the transcripts and supporting field notes to become familiar with the data.
- Establish initial coding.
- Identify the tentative themes.
- Revise the themes, checking against the codes and datasets.
- Define and name the themes.

Preliminary data analysis was conducted after each interview to determine whether changes to the interview guide were required. No changes were made to the interview guide during data collection. Preliminary data analysis was conducted in the original language of the interview, and themes and sub-themes were translated into English (if required) for further discussion and analysis. Members of the research team met regularly throughout data analysis to ensure consistency and to guide the next stage of analysis. Data coding was completed by Jingjie Yu and checked by Lingling Yang.

9.5.6 Ethical Issues

The protocol for this study has been approved by the RMIT College Human Ethics Advisory Network (No. BSEHAPP 29–15 XUE) (see Appendix 7) and the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine in China (B2016–104) (see Appendix 8). Data collection commenced after ethical approval was obtained at each site.

Participants were informed about the purpose of the study and were given the opportunity to ask questions. When participants were satisfied that they understood the project and had any questions answered, they were asked to provide written consent on the PICF (see Appendix

5). Both the participant and the researcher signed the consent form and the participant received a copy for their records. The PICF explains the voluntary nature of participation, the participant's right to withdraw from the project at any stage, and that data collected will stored in a non-identifiable, confidential way.

9.6 Study Rigour

The importance of a rigorous approach to ensure the trustworthiness of the research findings has been highlighted (254–256). Key concepts suggested by Guba (1981) (257) include credibility, transferability, dependability and confirmability. To ensure rigour, the following steps were taken:

1. Credibility: This refers to whether the study data collected are what was intended. The researchers who conducted the interview also performed transcription, and reviewed the audio and transcriptions several times to ensure familiarity with the content. Field notes were used to support the interview findings. The research team have CM clinical experience and met regularly (weekly or fortnightly as required) for peer debriefing. Negative cases analyses were used to allow for consideration of alternate explanations and ideas. While member checking (review of the transcript by study participants for accuracy) has been suggested as the gold standard for ensuring credibility, Sandelowski (2008) (258) suggested that the process for member checking may lead to confusion if participants change the information. Member checking was not used in this study.
2. Transferability: This refers to the generalisability of the findings to a similar setting. Detailed description of the findings from participant interviews will allow users to transfer information to a setting with similar characteristics to those included in this study.

3. Dependability: This step refers to the ability to obtain the same results should the work be repeated in the same context and manner. This was addressed in this study by providing a clear and detailed description of the methods. This allows for scrutiny of the methods and the possibile replication of the study.
4. Confirmability: This refers to the objectivity of data. This study used an audit trail to document interpretations, discussions and thought processes of the research team. This was evidenced through a clear history of coding and categorisation, and minutes of research team discussion.

9.7 Pilot Interview

One pilot interview was conducted separately to the main data collection, using the same inclusion criteria. The pilot interview allowed the researcher to develop an interview technique and test the interview guide for validity (see Appendix 4). Following the pilot interview, no revision was made to the interview guide. Data from the pilot were not used in the final analysis.

9.8 Data Security

In-depth interviews were audio-recorded and the recording transferred onto a password-protected computer for storage. The audio recording file label did not include identifiable information. Transcription was done by Jingjie Yu (for interviews conducted in Chinese) and Dr Meaghan Coyle (for interviews conducted in English). Transcriptions of recordings are stored on a password-protected computer. Transcriptions were de-identified by replacing real names with pseudonyms. The researchers have retained participants' names, pseudonyms and demographic information on a password-protected computer. The password is known only to the research team. Hard copies of de-identified transcriptions and field notes will be kept in a

locked filing cabinet. Data will be stored for a minimum of seven years from the publication date, as per the *Australian code for the responsible conduct of research* (259).

9.9 Results

Participant recruitment in Guangzhou, China occurred in July and August 2016, and recruitment in Australia was from September 2015 to November 2016. Recruiting participants in Australia was more challenging. While it was anticipated that 20 participants would be recruited from each site, the saturation of qualitative data provided by participants occurred before this target was reached, and recruitment was ceased.

9.9.1 Demographic Information on the Participants

Sixteen participants in Guangzhou, China and five participants in Melbourne, Australia were recruited in this study (see Table 9.1). Nine participants suffered from psoriasis vulgaris with duration from 2.5 months to 24 years. The duration of 10 participants with chronic urticaria was from eight months to 10 years. Two participants were affected with both conditions and the disease duration was from three months to four years. The number of female and male participants was almost equal (11 females, 10 males). The age of participants ranged from 20 to 59 years. All but one participant received CHM in China and were Chinese, with eight originating from Guangdong Province (Canton) in southern China. Most participants were tertiary educated. Most participants were professionals, except for six students. Two respondents were CM practitioners.

Table 9.1: Demographics of Participants in Qualitative Interviews

No.	Disease	Age	Gender	Duration	Ethnicity	Education	Employment
CHN 001	Psoriasis/ Urticaria	20	Male	4/2 years	Chinese (Cantonese)	Graduate	Student
CHN 002	Urticaria	29	Female	4 months	Chinese (non-Cantonese)	High school	Education
CHN 003	Psoriasis	34	Male	3 years	Chinese (non-Cantonese)	TAFE	Unemployed
CHN 004	Urticaria	30	Male	8 months	Chinese (non-Cantonese)	Graduate	Manager
CHN 005	Urticaria	36	Female	8 years	Chinese (non-Cantonese)	Graduate	Marketing
CHN 006	Psoriasis	54	Male	9 years	Chinese (Cantonese)	High school	Marketing
CHN 007	Psoriasis	59	Male	7 years	Chinese (Cantonese)	High school	Lift worker
CHN 008	Psoriasis/Urticaria	24	Female	3 months/2 years	Chinese (Cantonese)	Graduate	Cinema management
CHN 009	Psoriasis	30	Female	2.5 months	Chinese (non-Cantonese)	Graduate	Publisher
CHN 010	Psoriasis	35	Male	5 years	Chinese (non-Cantonese)	Graduate	Accountant
CHN 011	Psoriasis	29	Male	8 years	Chinese (Cantonese)	Graduate	Finance officer
CHN 012	Psoriasis	56	Male	5 years	Chinese (Cantonese)	Graduate	Law enforcement officer
CHN 013	Psoriasis	36	Female	7 years	Chinese (non-Cantonese)	Post graduate	University lecturer
CHN 014	Urticaria	30	Female	10 years	Chinese (non-Cantonese)	Post graduate	Doctor
CHN 015	Urticaria	30	Female	5 years	Chinese (Cantonese)	Post graduate	Doctor
CHN 016	Urticaria	30	Female	10 years	Chinese (Cantonese)	TAFE	Clerk
AU 001	Psoriasis	41	Female	24 years	Caucasian	Post graduate	Student
AU 002	Urticaria	21	Male	2 years	Chinese (non-Cantonese)	Post graduate	Student

No.	Disease	Age	Gender	Duration	Ethnicity	Education	Employment
AU 003	Urticaria	25	Female	3 years	Chinese (non-Cantonese)	Post graduate	Student
AU 004	Urticaria	23	Female	6 years	Chinese (non-Cantonese)	Post graduate	Student
AU 005	Urticaria	24	Male	2 years	Chinese (non-Cantonese)	Post graduate	Student

9.9.2 Themes Emerging From the Interviews

Through 'open coding' line by line, themes emerging from the experiences of participants living with a chronic skin condition included 'experience of symptoms', 'a bleak future', 'the learning curve', 'living with disease', 'pros and cons of conventional treatment' and 'paying for relief'. Themes about participants' motivators to seek CHM as treatment were identified. They were categorised into 'beliefs and experience', 'want an alternative' and 'practitioner selection'. Six themes related to participants' experiences of using CHM for chronic skin conditions were discovered: 'tailoring the treatment', 'response to treatment', 'managing CHM', 'concern about CHM' and 'value for money'.

Experience of symptoms

Participants suffered from the symptoms that are typical to these two conditions. Participants recalled how their symptoms first occurred, starting with small lesions such as red spots, which then enlarged to erythema. In one participant with psoriasis vulgaris, this gradually spread to cover the whole body. The erythema often occurred with skin scaling and participants felt their skin was dry and itching. When the scales were removed one participant experienced tight skin in the lesion area and was eager to apply moisturiser, especially in winter.

The most annoying symptom was pruritus for people with urticaria, which was excruciating for most participants. Participants described the sensation of urticaria as if their whole body was bitten by mosquitoes at the same time, as a burning sensation, or as if they were stimulated continuously with needles. Most of them could not stand this feeling:

> Just imagine your whole body is bitten by many mosquitoes, you feel uncomfortable even bitten by one, just imagine the feeling that you got full body of rash bitten by them. (就是你想象全身很多蚊子咬的那种感觉，就是你一个蚊子包你都会很难受，你想象全身的蚊子包那种感觉). (Participant CHN 005 chronic urticaria)

> And the itchy feeling come with heat, you feel very itchy and hot, a little bit, not too obvious, just you can feel it. (而且有热热的那种痒，就是那种热辣的那种痒，有一点点，不是很明显啊，就是可以感觉到有种热辣的那种). (Participant CHN 005 chronic urticaria)

Wheals often occurred after meals or at night, and disappeared within one hour. The frequency of symptom occurrence differed over time and symptoms came every day at the peak time. In addition to wheals and pruritus, a few participants mentioned that they suffered from gastrointestinal symptoms, such as diarrhoea, and encountered breathing difficulties:

> I felt chest tightness. As I told another doctor, I suffered from laryngeal oedema and I said my symptoms were very serious. Previously, I had some small red dots on my body, but they become more serious this time. Besides, my lips were swollen, my eyes were swollen and my face was swollen as well. Then, I felt my chest tightness. (就是胸闷，然后就是，那个那个，然后后来那天去看另外一个医生说，可能是喉头水肿，然后我说这个就已经很严重了，然后以前呢，那次，第一次发，也就是身上有些小红斑，就是小红团，结果现在这次发呢，就后面就很严重，就是嘴唇肿，眼睛肿，就是脸肿，然后就是，又胸闷). (Participant CHN 005 chronic urticaria)

Participants with both chronic urticaria and psoriasis vulgaris emphasised the recurrence of disease, or that the symptoms came and went. Generally, compared with the long-term manifestation of psoriasis vulgaris, the symptoms of chronic urticaria occurred rapidly and were relieved quickly. For example, wheals often disappeared within one hour. However,

frequent occurrence of symptoms was commonly observed in participants with chronic urticaria.

Participants found several things triggered or aggravated their skin conditions. For psoriasis vulgaris, participants suffered from exacerbation of symptoms after drinking alcohol, staying up late or eating seafood. During the winter, the symptoms could be worse. It is interesting to note that one participant with psoriasis vulgaris experienced exacerbation before and during menstruation:

> Another factor is period, I assume it has big influence … I mean the menstrual period, one week before period and in that week, new lesions might occur. (还有个就是经期，我觉得影响蛮重的…就是生理期，生理期的前一周，和生理期的那一周，就明显的会长新的出来). (Participant CHN 009 psoriasis vulgaris)

For chronic urticaria, the occurrence of symptoms could be triggered or aggravated by temperature change, diet, sleep and anxiety. Seafood was a common factor that caused the condition. One participant with chronic urticaria suffered from wheals and pruritus after eating calamari. The wheals and pruritus occurred easily due to temperature or mood changes, such as anxiety. Intermittent sleep with low quality also contributed to one participant's condition:

> Yeah, [eating] those squid, octopus, etc, will trigger [urticaria]. (对，就是鱿鱼什么的，章鱼啊，那种都会). (Participant CHN 015 chronic urticaria)

A Bleak Future

All participants expressed concerns about their futures to varying degrees since being affected with psoriasis vulgaris or chronic urticaria. Most participants had a negative reaction to the disease diagnosis. For psoriasis vulgaris, participants felt dysphoric, fearful and even desperate about their futures due to the disease. One woman experienced a flood of emotion when she heard the diagnosis of psoriasis vulgaris. She cried immediately and was confused

about the reasons she had been inflicted with this condition. Another participant felt preoccupied when she was diagnosed:

> I think I would always want to blame myself or wonder what I'd done or something like that … I was very preoccupied with wondering things like that. (Participant AU 001 psoriasis vulgaris)

Participants felt depressed about their appearance and anxious about other people's misunderstandings of the contagiousness of psoriasis vulgaris. A few participants became irritable since suffering from the disease. Moreover, participants were uncertain and worried about disease inheritance and progression in the future:

> I think … people usually think *niu pi xuan* (psoriasis) is quite severe, and are not sure its infectiousness. (我觉得……正常人的理解会觉得牛皮癣是很严重的吧，而且还不知道传不传染). (Participant CHN 009 psoriasis vulgaris)

> First of all, I have mentioned before, whether it's genetic? Secondly, I worry about comorbidity. As I am young now, the disease doesn't affect me too much now. However, it could influence other parts of my body later, which brings more problems. Thirdly, I can't imagine how it's going on when I become older. I have considered these issues. (第一个就刚刚说到的，不知道它会不会有一个遗传性，呃然后第二个，第二个就是说，后续的话，因为现在毕竟我，现在来说呢还年轻，它反复起来其实问题也不大，可是我也担心它如果将来会不会有严重性的发展，其实我了解到它后续的那个发展，可能会延续到四肢啊或者身体的其他部位，那就可能会更加麻烦一点，然后第三个就是再往后发展的话，特别是到了年纪比较大的时候，它的发展情况又是怎么样自己也没有个底). (Participant CHN 011 psoriasis vulgaris)

Similarly, participants were not sure when the disease would go and whether it could be cured. It became most difficult for them to accept the relapsing nature of the disease, prompting anxiety about work intensity or QoL. One participant also expressed concern about development of other health conditions in the future. This participant was aware that other conditions, such as cancer, hypertension, are known comorbidities of psoriasis vulgaris:

> Hmm it is one concern that when it can be cured, another concern is whether it could be cured? Because not all the patients can be cured, that doctor said, someone may not … one patient friend told me, he even doesn't know what is relapse (laugh) because the condition never went (嗯什么时候好是一个问题，还有就是能不能好也是个问题？因为不是所有人都好的，那医生说，可能有些人他就没有……因为有个病友就说，他就说，我连什么叫复发都不知道（笑）。因为从来没有好过). (Participant CHN 009 psoriasis vulgaris)

For chronic urticaria, participants felt their diagnosis was inconceivable and they felt dysphoric and even desperate about the diagnosis. One woman thought that her face was disfigured by wheals and likened her appearance to a pig's face. Participants were worried that they could not concentrate on work and study due to the recurrence and long-term manifestation of pruritus or wheals. Major concerns for their future included laryngeal oedema, as mentioned by one participant. She was anxious that it could threaten her life:

> Nowadays my most concern is not my skin, the wheal, but laryngeal oedema. I am worried about that if it happens suddenly when I am sleeping, I will die. Several days ago, a western medicine doctor prescribed steroid medication, which could be used when I can't take a breath. Then I can call hospital for first-aid. I feel horrible about this. Does laryngeal oedema mean the disease becomes more serious? （我现在困扰最大的啊，就是，我反倒不在那个皮肤，那个风团了，我现在困扰最大的是这个，我担心喉头水肿。因为我，前两天，有时候晚上睡觉睡着睡着我说，我会不会睡着睡着，突然喉头水肿了，然后我就，就过不了气，就人就完蛋了，就担心这个东西，所以后来那个时候，有隔西医，有个看西医的给我开的那个激素药嘛，如果真的晚上突然发现呼吸不行了，赶紧激素下去，然后打，然后去医院急救，就听起来我就觉得很恐怖，所以现在对我困扰最大的就是这个，真的就是到了这个喉头水肿这个，到底是不是这个病更严重了。). (Participant CHN 005 chronic urticaria)

Participants who suffered from both conditions at the same time reported becoming more fearful and dysphoric about psoriasis vulgaris. Unlike chronic urticaria, they thought the image of psoriasis vulgaris would exist persistently, perhaps even for their whole lives.

For both psoriasis vulgaris and chronic urticaria, participants were uncertain about the possibility and time required to achieve cure for the diseases. They might have to continue using medication all the time as the symptoms came and went, which could result in side

effects. The uncertainty of disease severity and treatment effects made participants anxious, dysphoric and desperate. In terms of diet, they had to consider the possibility that food could trigger or exacerbate the disease. This undermined their confidence and caused them to have concerns about their future.

However, three participants were accepting of the disease, despite the impacts the conditions might have on their lives in the future. One participant considered psoriasis vulgaris as only a skin problem that did not affect internal organs. Similarly, the other participant did not regard chronic urticaria as a significant health issue. Through knowledge gathered from the internet, the third participant had already anticipated the diagnosis of psoriasis vulgaris. He thought it was most important to receive treatment as soon as possible.

The Learning Curve

Most participants had little knowledge about the condition before its onset, except for two participants with chronic urticaria, both whom were doctors. One doctor considered that low quality sleep contributed to her disease, as she had to take care of her baby during the night. She perceived that treatment should focus on improving constitution and enhancing healthy *qi* through CHM (according to her professional knowledge). The other doctor researched the disease and treatments using textbooks or advice from teachers.

Other participants began learning about the condition and treatment through the internet. For instance, participants with psoriasis recognised that the disease was not contagious, and CHM might be more beneficial than WM. Participants with chronic urticaria 'listened to their body' and noticed that alternative exposure to coolness and warmth would trigger the skin disease. All participants began to pay attention to self-management. One participant sought supplementary treatments by themselves, using products such as grape seed.

Living with Skin Disease

Both psoriasis vulgaris and chronic urticaria had significant impacts on participants' daily lives. The primary concern for participants with psoriasis vulgaris was physical disfigurement. One participant described his embarrassment when a large amount of scale fell from his skin in public, which might not be accepted by others easily. Another woman also described her embarrassment in a dancing class because her lesions of psoriasis vulgaris could be observed when she was wearing a leotard. Clothing was described as a factor that prohibited a man from playing sports:

> I was in a dancing class and … I was embarrassed to wear the leotard because … you could see some psoriasis. (Participant AU 001 psoriasis vulgaris).

For many participants with psoriasis vulgaris, it was not easy to interact with other people. They were afraid to talk about their condition and avoided their social networks. The large amount of erythema and scale made other people feel uncomfortable and they were concerned about its contagiousness. One participant mentioned that leisure activities with friends were also reduced due to the disease. The main leisure activity in his community was swimming, but he did not wish to join in:

> It will also have impact on appearance. When other people see you, they are also afraid of it, the peeling skin, it always falls off, so it is, like this, and then people know, know you have this skin condition. (然后也影响外观呢，别人看到你也怕一点呢，老是掉皮，这样子啦，就这样子啦，现在就是人家就是知道，知道你这样子). (Participant CHN 007 psoriasis vulgaris)

> For example, we live in a coastal area, so they would like to go swimming; I just went with them for very few times. (比如说我们那里近海边，每次那么出去游泳的话，去玩的话都很少出去). (Participant CHN 003 psoriasis vulgaris)

Psoriasis vulgaris also influenced general health, such as a general lack of energy. Some participants had to stop working, while one reported losing their job due to the disease. For this participant, the economic burden was significant after the loss of income, with a child to

be raised. Another impact on participants' daily lives was sleep. The large amount of scale in the bed made participants feel uncomfortable, making it difficult to sleep. In summer, this discomfort worsened due to increased perspiration. Participants scratched the skin in response to itch, which might cause bleeding and pain. If they experienced pain they applied ointment. However, the ointment made participants feel sticky during sleep. These experiences influenced their sleep. In addition to the effects on sleep, a few female participants held concerns about pregnancy or the potential for their babies to inherit psoriasis vulgaris:

> Sometimes feel itchy. Right? … On top of that, I always have scale, falling on the bed … I have to clean it up every time … It is quite hot and humid these days, the scale mixed with perspiration, it is very sticky, very hard for me to fall asleep. (它有时候痒嘛，是不是？ … 嗯，再加上呢，你老是脱屑，它这个皮老是在那，全部都是个在那个床上啊，每次都要清理的 … 这段时间在湿热天，它掉到那里，出点汗，一沾酒是沾到身上，也是睡不着). (Participant CHN 003 psoriasis vulgaris)

> Another concern is that, I am worrying about my newborn baby, afraid of the genetic influence. (还有因为刚生完小孩嘛，怕这个有遗传，有影响). (Participant CHN 013 psoriasis vulgaris)

For chronic urticaria, participants felt absent-minded and could not concentrate on work due to bothersome symptoms, such as pruritus or gastrointestinal changes like cramps, bloating and diarrhoea. This resulted in low work efficiency. For example, participants tried to control pruritus to help them concentrate on work or study. For one participant, the impact was significant and affected their university entrance examination, resulting in another year of study. Gastrointestinal changes like abdomen pain and diarrhoea forced one participant to take sick leave, and try multiple therapies, such as medication and moxibustion, to relieve serious diarrhoea:

> For a long time, that is, you can reduce the feeling of itch by your mind and thoughts. You will think that do not care too much about it, but there is no way you cannot prevent feeling itchy, or ignore it, and if feel painful, you will not unconsciously touch it, but for itchiness, you will touch it unconsciously. If you touch it, it will be more itchy, and then it will spread. (时间长了，就是，你可以用意念趋势去减轻它，不太在意它，但是痒不可以，你没有办法忽略它，而且这个疼不会下意识地碰它，但是痒你会下意识地用手去碰它，然后你一碰它，它就更痒，然后它会扩散). (Participant AU 003 chronic urticaria)

> The most serious thing for this time was the symptoms of gastrointestinal reaction, it was really serious, I took some days off from work, and I could barely handle my daily life (laugh) … You see, too many times of diarrhoea, maybe more than 10 times a day, just long-lasting watery diarrhoea, and it was not relieved after taking pills, so I took medicine, and then had moxibustion, anyway, just keep warm at home, I tried everything I could (laugh), took medicines and other stuff, it took three to four days to feel better. (最严重的就是这次是有这种胃肠道的症状，这个是真的很影响，就是就已经请病假了。然后就完全生活很难自理（笑） … 你说，腹泻次数太多了，一天可能十几次，就是持续的水样泻，然后就是吃药也不能缓解么，然后就吃药，然后艾灸，反正在家里面然后什么持续保暖啊，然后各种吧（笑），就喝药或者是各种搞了一下，三四天吧，这样才收下来). (Participant CHN 014 chronic urticaria)

In addition, pruritus made it difficult for them to fall asleep. Disrupted sleep would have further influence on study or work efficiency. As sport could potentially trigger chronic urticaria, participants took part in fewer sports activities to avoid symptoms like wheals or angioedema:

> It is greatly related to sleep. Now I remember, because if itch occurs when [I] sleep at night, I can't sleep, especially sleep, the light sleep, at the beginning period of sleep. It will have great influence and last. (睡眠是一个很大的关系，才想起来，因为晚上睡觉的时候它会很痒，就是睡不着，尤其是睡觉，浅睡眠，就是你开始睡觉的那一段时间，它会影响很大，它会一直痒). (Participant AU 003 chronic urticaria)

A few participants with chronic urticaria felt embarrassed about their appearance and reluctant to participate in social activities. One woman pointed out that her condition was misunderstood as a sexually transmitted infection by the senior people with minimal knowledge of the condition:

> When I first have this, I was scared about seeing people, because they will laugh at me, and people see the wheals on my skin, they may think I have sexual disease … The first is that, when I have the symptoms of urticaria on my face, my face will look very ugly. Besides, sometimes there will be much redness on my arms; they may think you touched something not clean especially the old, sometimes … some old people are always mislead by the media, for example, sometimes when I go to the hospital, they will say such a young girl have caught the sexual disease, which is embarrassing. (基本上是不敢太出去见人的，因为大家看了都会笑，然后平时走在路上的时候，人家看我身上长那种风团、风块，他会认为我是不是有性病之类的玩意儿 … 第一个就是，因为我脸上得荨麻疹的话，会肿成像猪头一样特别难看。然后第二个就是有时候我身上胳膊都出来一片一片的红块啊，她们就会认为是不是沾了不干净的东西，尤其是一些老年人，就是有时候跟他们 … 有些老年群体受新闻误导比较多，比如有时候去医院的时候他们就是说一个小姑娘年纪轻轻得什么性病就是这样的，挺尴尬的). (Participant AU 004 chronic urticaria)

Some participants were concerned about the occurrence of urticaria during their pregnancy because they had to stop taking medication and suffer the painful symptoms. They were also unsure whether the condition could be hereditary.

Paying for Relief

Due to the disease, participants had to spend money to relieve the symptoms. The cost of WM treatment was acceptable for one participant. However, others thought the expense of WM treatment was high, especially for long-term use. They could not afford it without medical insurance, particularly students. Other costs included the expense of supplementary agents such as grape seed, which one participant believed was beneficial.:

> To talk about health insurance, medical fee, you see if I use that ointment, like a moisturiser or a desonide ointment. Each of them are more than 20¥. But they are free for me now. (医保的话，那你费用，你看如说我涂那些东西，一个润肤的，一个地奈德都二十几块一那个什么，全都是人家免费供给我的). (Participant CHN 007 psoriasis vulgaris)

Pros and Cons of Conventional Treatment

All participants recognised that the advantage of WM treatment was the rapid onset of relief. WM treatment (for example, corticosteroid ointment) could reduce skin lesions of psoriasis

vulgaris and improve skin condition significantly, but relapse was quite common. Participants had to persist with the treatment for a long period. The experience of using some WM agents was negative. Participants felt that coal tar looked disgusting and smelt bad:

> But I have to use this ointment (clobetasol propionate compound ointment) very frequently … if I use it today but not tomorrow, it will be fine. However, I must use it the day after tomorrow. (就是说你这个药膏 (复方丙酸氯倍他索软膏)，你得总抹 … 就是说比如说我今天抹了，第二天你没抹，可能问题不大，但是第三天就一定要抹了). (Participant CHN 013 psoriasis vulgaris)

For chronic urticaria, participants pointed out that antihistamine could relieve pruritus instantly, but the effect was short-lived. Wheals and pruritus came again on other days after taking medication. In addition, one woman described that antihistamine lengthened her next menstrual period:

> As time interval (for onset of relief) getting longer and longer and it cannot prevent attacking at next time. It means that you taking the medicine today ensure the effects today or tomorrow, only these two days. (越来越长，而且它不能够防止就是下一次，就是你今天吃了这个药只能保持今天或者明天，这两天的时间). (Participant AU 003 chronic urticaria)

Beliefs and Experience

Participants chose CHM as treatment for psoriasis vulgaris and chronic urticaria based on their beliefs of CHM or personal experience using CHM. The use of CHM is a part of the culture and way of life for people born and living in Canton. It is a common for Guangzhou residents to have herbal soup and herb tea. One participant with chronic urticaria mentioned that her first experience with CHM was as a child. Her parents made soup using various herbal formulae that were adapted according to the weather (this fits with the CM theory of the external environment affecting the individual's health). Herbs were easily accessible in the herbal pharmacy or herbal market. For local Cantonese participants, the choice of CHM was influenced by cultural background. Participants originating from outside Guangdong

Province also trusted in CHM and were influenced by their family members. One participant with chronic urticaria had belief in CHM because she could see the raw herbs to be used in the decoction. The reputation of the hospital was a reassuring aspect for participants seeking CHM:

> Especially in Guangdong, it is very common that people in Guangdong really prefer to cook soup. That is the culture of soup. Many people cook soup … in summer … like the summer solstice, they used cicada slough, Chinese watermelon and pearl barley. Sometimes look at the condition of the stool, if they feel uncomfortable, they will buy Glabrous greenbrier rhizome soup, eat dishes, what other else is eating the food that is nourishing, like the ginseng … nourishing. (而且更广东嘛，广东不是很喜欢煲汤嘛，就是那种汤文化。就很多人就会，就普通百姓也知道哪些能祛湿啊。就我们中医理论的祛湿，像我妈也懂啊。夏天…就是什么天啊，就夏至什么的，他们就用蝉蜕啊，冬瓜，加薏米。有时候大便怎么样，他们自己感觉不舒服也会买土茯苓煲汤，什么的。滋补的也会啊，花旗参啊，清补的也会). (Participant CHN 015 chronic urticaria)

> Yes. Since I was child, my family have more belief in traditional Chinese medicine. (对，从小我们家人就比较信任中医这个方面). (Participant AU 003 chronic urticaria)

The selection of CHM was also influenced by personal knowledge. Participants obtained the information on CHM from the internet, books or professional medical study. They believed CHM could improve personal constitution and treat the root (underlying factor) of the disease, since CHM emphasised individual treatment and general regulation for the whole body. Participants expected that CHM could reduce the relapse of their skin disease with fewer side effects. Moreover, the factor motivating participants to seek CHM treatment was their personal experience of using CHM for other conditions and achieving satisfying results:

> That's right, if they've experienced this and feel good, they will believe it. (对，如果他们体验过这个东西，觉得比较好，他们就比较信这个东西). (Participant CHN 015 chronic urticaria)

> More confident than western medicine at least. As CHM mainly improves constitution, treat the root (underlying factor) of disease, it should be. (至少比西医有（信心）很多，因为中药主要还是从改善体质，治本吧，应该是). (Participant CHN 009 psoriasis vulgaris)

In addition, participants showed particular interest and fascination with herbal medicine. One woman with psoriasis vulgaris described the whole experience of using CHM, which she really enjoyed:

> I think I was open but I did have a particular fascination with herbs … so I would, probably would've been disappointed if I didn't get herbs … although the taste and the smell was … not very nice, I actually really enjoyed the whole experience of … of getting the bags of herbs and making the decoctions. (Participant AU 001 psoriasis vulgaris)

Want an Alternative

The factors that motivated participants to choose CHM included the unsatisfying AEs of WM treatment. For instance, the blood test of one participant with psoriasis vulgaris indicated abnormal liver function after taking MTX. He decided to choose CHM as an alternative:

> Because I take the methotrexate, at that moment, the doctor didn't tell me it affected liver when he prescribed it, I took for a while, and the next time I went there, another doctor asked me to take a blood test, the result showed the value of transaminase was too high, he told me to stop taking it, then I asked, he told me it affects the function of liver. Then I didn't dare to take it, and stopped it. I did not take it anymore from then. I came here, and ask prescription here, starting to take the Chinese medicine. (因为吃那个甲氨蝶呤，吃了，当时，他没有告诉我说吃那个甲氨蝶呤片对肝那个影响，他开的时候也没说，连续吃。后来，再去开药的时候，有一个医生就是说，你先去验验血，一验血，那个转氨酶升的很高，那个他说你你要停了，不能吃了，那我才问，他说影响肝功能嘛，影响那个，那我就不敢吃了，那我就转过来，就没有再吃了，我就停了，那个药我就没有再吃了，我就过来，过来这种中医院这边开，吃中药). (Participant CHN 006 psoriasis vulgaris)

Due to the side effects of WM treatment, participants wanted an alternative to manage the symptoms of psoriasis vulgaris or chronic urticaria:

> I am not particularly dependent on western medicine; I do not want to continue to take western medicine, because I think it has some impact on my menstrual period. The period may turn to be longer. (本身我对西药不是特别的依赖，我不太想一直服用它，因为我觉得它有些影响我的经期。我的经期会，就时间会变长). (Participant AU 003 chronic urticaria)

Practitioner Selection

Through the interviews, participants also described how they came to choose their CM practitioners, which was also related to participants' motivators to seek CHM. Participants selected the CM practitioner based on the practitioners' profile on the internet or recommendation by other patients and even WM doctors:

> Hmm … website of Hao dai fu (laugh). (额…好大夫网站（笑）). (Participant CHN 009 psoriasis vulgaris)

> Well, I will absolutely see the doctor's resume, that kind of reference. (额，肯定是看医生的简历，那个介绍). (Participant CHN 007 psoriasis vulgaris)

Tailoring the Treatment

The administration of CHM included oral or topical use, depending on the aim of treatment and participants' preferences. Oral use of CHM decoction was commonly observed, which was often brewed by participants or their family members. The decoction could be applied topically as well, such as in a bath to remove scales of psoriasis vulgaris and soothe the dry skin. Tablets and granules were chosen by participants who were unable to make CHM decoctions, which was more convenient. Individual treatment was highlighted during the treatment and modification of formula was applied if needed. For instance, the CHM formula was modified if new lesions occurred or when the participant was menstruating. CHM was often combined with WM treatments like corticosteroid ointment or antihistamines:

> Hmm I just use it locally … only for lesions. (额我一般就擦洗 … 就有问题的地方才擦洗). (Participant CHN 009 psoriasis vulgaris)

Response to Treatment

With the exception of three participants, all others experienced positive responses to CHM treatment. For most participants, CHM improved symptoms of disease significantly, such as scale and erythema for psoriasis vulgaris or wheals for chronic urticaria.

For psoriasis vulgaris, two participants mentioned that CHM reduced the scale obviously, with the size of erythema shrinking for one participant. Three participants pointed out that CHM could prevent the occurrence of new lesions and control disease progression, although they found no dramatic improvement for existing lesions. No side effects arising from CHM were mentioned by participants. When CHM was combined with acitretin (a retinoid drug), it reduced the skin dryness of one participant.

> Hmm, I found my skin looked good on the day before I came here for subsequent visit. That is scale, the erythema became atrophic. In general, improvement occurred. I felt quite pleasantly surprised at that time (laugh). (嗯，那时候过来复诊的前一天，发现皮肤好很多。就是皮屑，就是那个斑有萎缩的症状，就是好转了。那时候就特别的惊喜（笑）). (Participant CHN 009 psoriasis vulgaris)

In addition to the improvement of skin symptoms, CHM also made participants with psoriasis vulgaris more energetic, relieved emotional discomfort and reduced the frequency of common colds. Once the usage of CHM was stopped, the symptoms of one participant returned. The efficacy of CHM varied due to differences in preparation. One participant experienced better efficacy with decoction than granules. However, another participant thought granules provided better efficacy because he could guarantee the intake of required dosage due to the convenience of usage. In one participant with chronic urticaria, taking CHM treatment for one week resolved symptoms of wheals and pruritus, although she did not indicate whether they recurred.

Unlike WM treatment, CHM had no impact on her menstrual period. Relapse of urticaria symptoms for participants was also reduced by CHM. One participant achieved clinical cure (no symptoms) for up to five years after taking CHM. In some cases, CHM in combination with WM controlled disease progression and reduced the usage of WM gradually. In addition to improvement in skin condition, CHM was beneficial to general health, with some participants describing an improvement in their mood. However, a few participants found it took a long time to achieve improvement in symptoms with using CHM. Further, the symptoms might return once the treatment was ceased. Gastrointestinal reaction after taking CHM was mentioned by one participant.

> For example, like the formula prescribed by Professor X … for instance I have to take Western medicine once in two days, which means the symptoms can be gone only when I take it after one day. Then I took the Chinese medicine from Professor X, I may take it once in three days, and … four days later. Last time (five years ago) it was cured by this method. Just take a rest, and the rest time became longer, I found that I didn't have to take the Western medicine. It can be cured only by using Chinese medicine. (比如说那个…X 教授的那个，给我开的药，就是，比如说我以前是两天我就要吃一次那个，就是，隔一天我就要吃一次西药那才能够消下去，然后吃 X 教授的（中）药，吃完可能就会隔两天，然后过段时间可能隔三天，我上次（五年前）也是这么好的，就是隔,隔，然后间隔的时候越来越长，我发现不用吃西药了，光吃中药也好了). (Participant CHN 005 chronic urticaria)

Not all participants reported benefits. One man with psoriasis vulgaris reported no change in the lesions but experienced improvement in his general health (such as increased energy). This was the reason that he persisted with CHM. Another woman with chronic urticaria also had no improvement in skin symptoms. She insisted on using CHM due to the reputation of the CM doctor. Moreover, the symptoms of one man with chronic urticaria got worse, with eruption of wheals after taking CHM for one week. However, he thought it might be a sort of initial reaction to CHM. He felt it was necessary to wait for improvement over time.

Based on personal positive treatment experience, participants wanted to spread the word and recommended CHM to more patients suffering psoriasis vulgaris or chronic urticaria. One participant, who was a CM practitioner, pointed out that she would take patients' individual conditions into consideration when recommending CHM, such as patients' age or occupation.

Managing CHM

The most common preparation type of CHM prescribed by CM practitioner was decoction. In addition to traditional CHM decoction, CHM products included granules, capsules and tablets. They became another option for people seeking CHM as treatment. Participants suggested that granules were more convenient than CHM decoction. The granule method was handy and easy to make for drinking, which was not as time-consuming as decoction. Participants could follow the treatment scheme easily.

Some participants thought following CHM regimes was not burdensome or difficult. However, some thought it was hard to manage. For instance, participants mentioned that it was inconvenient and time-consuming to make the CHM decoction. They had to monitor the time for making CHM decoction. The taste of CHM, regardless of decoction or granule, was the most unacceptable factor for most participants. They found it unpalatable to drink because of the bitter taste and the presence of granules that did not dissolve into liquid. Participants felt nausea and had no appetite:

> It is not easy to make the decoction. Because, like my family, the old people can make the decoction. If there is no old person at home, after going back home for dinner, and then making the decoction, it will waste a lot of time. However, for the granule, it has not been proved that has effect, and is expensive as well. The granule seems to be afforded by patients themselves. And then because this is personalised treatment, a Chinese herbal medicine product is certainly not so good. For personalised treatment, you have to prescribe formula, for the formula, the granule is more expensive, and then, the efficacy is uncertain. I am not sure the efficacy of granule when compared with decoction … But it's really troublesome to make decoction. But if you want to have a try, by the way I have not tried it before. Is

there some kind of service for making decoction? (就是不方便要煲药。因为像我家里有老人家就可以煲，那家里没有老人家，下班后回去做饭，吃完然后再煲药，那也很花时间。但是颗粒剂的话，又不确定它的疗效，而且又贵很多，颗粒剂好像是自费。然后因为这个是个体化治疗，中成药肯定没那么好啊。那你个体化治疗的话，你也要配方，配方的话，颗粒有又比较贵，然后，疗效就…你…不确切嘛。我不知道这个方这样吃，跟药材煲出来…但是你药材煲确实是挺麻烦的。但是如果你要剂的话呢，我倒是没试过，不是说有那种代煎吗？). (Participant CHN 015 chronic urticaria)

I mean, those, granules mixed up with multiple CHM herbs, it tastes worse than the decoction, the dreg, really hard to swallow … The granules cannot be dissolved completely, they were underneath, you were not sure whether eat them or not, and I ate them, felt like vomit[ing] after that. (我说的颗粒是那种很多中药混合的那种颗粒，真的你捞出来然后吃那个，真的比那个汤药难喝多了，后面那个渣子，根本就很难吃下去……就它一般不可能完全溶解，它都是会在后面，会有一些那种剩下的，吃也不是，不吃也不是，然后就吃完，然后就觉得吃了就想吐的那种). (Participant CHN005 chronic urticaria)

Adherence to CHM decreased due to a lack of access to some herbs, busyness at work or study and personal preference on the preparation type of CHM. For example, one participant described that she could not purchase all the herbs (ingredients) shown in the prescription once she moved location due to study. She preferred to use CHM capsules instead of decoction. In addition, one woman mentioned that she was afraid of raw herb formula that contained insects as ingredients. It was unacceptable for her to drink such CHM. She preferred CHM granules:

The doctor asked me whether I drunk decoction, then I had a look at the formula, many insect ingredients were involved, because I am scared of insects, so I told him that I would have the granule, they were convenient as well. (医生当时也问我他说你是要煎煮的，然后我看了一下药方，虫类的特别多，然后我这个人比较怕虫，所以我跟他说我就要颗粒的，也比较方便). (Participant AU 004 chronic urticaria)

Concern about CHM

It was believed by most participants that CHM was safe and had fewer side effects compared with WM. However, a few participants were still concerned about the side effects of CHM

after long-term use. They assumed that CHM had toxicity and could affect their health (for example, liver dysfunction):

> Although CHM may regulate your health, it is also a burden to body if you take a long time, because CHM involves the toxicity and pharmacological effects, my main concern is that if I take the CHM every day for a long term, it may bring some pressure and burden to body and other aspects. Because I have concern about the toxicity of the CHM, I sometimes worry about this … mainly from friends or relatives, anyway we have an old saying 'every medicine is toxic', so this is my main concern, because it always has some side effects after long time accumulation, regardless of what substance. (因为毕竟吃中药它虽然会调理身体，但是长期吃中药对身体来说也是一个负担，因为中药它毕竟它的那个药理性或者说毒性还是一定有的，主要也会担心它长期，每天喝这个中药的话，对身体，各个方面会有一定的压力和一定的负担，因为我自己也担心就是中药它也会有那个一定的毒性，会有这方面的担心 … 主要是从朋友啊亲戚方面知道，反正我们有句古话叫'是药三分毒'嘛，所以就主要是这方面担心，因为所有的东西它累积长了时间，它始终会有一定的副作用嘛，不管是什么样的东西). (Participant CHN 011 psoriasis vulgaris)

In addition, one participant pointed out that some patients had less trust in the preparation of CHM. They thought the valuable herbs would be removed if the hospital made the decoction for them:

> For many old people, they would rather make decoction by themselves than ask anybody else to do it, even though they do not have the tools to decoct at home, they will buy or borrow, just not to ask the hospitals to do it. They think the hospitals may cheat on them, for example, there are many precious herbs in the prescription, but in reality they only add a little into the decoction. (很多上了年纪的婆婆和爹爹们，他们都宁愿回去自己煎都不会让人代煎，就算是家里也没有这种煎药的工具，他们也会就是说想方设法的去借或者去买，就是不会代煎，就是他们就会觉得医院会坑他们，就是开的药方放了很珍贵的中药，但是实际上煎的时候只给你加那么一点点). (Participant AU 004 chronic urticaria)

One participant with chronic urticaria had more trust in manufactured CHM products, such as granules, than CHM formulae with raw herbs prescribed by CM practitioners. However, one participant perceived the efficacy of granules might not be comparable with decoctions. This was because preparing granules involves less work than boiling herbs in decoction:

> It seems that granule does not have effects. Among the herbs of CHM decoction … that kind of ingredients, due to interaction, it may have effect, but the granule is to put each granule together and mix with water, I suppose it will not generate effects. (就是它那种作用出不来啊。很多药物之间会有…那种成分，在相互作用，可能会有那样子的，但是你那个颗粒就是形成单独的颗粒，冲的话，我觉得你也不会产生什么). (Participant CHN015 chronic urticaria)

Value for Money

Participants held various views on the cost of CHM or CHM in combination with WM. Generally, the cost of CHM was acceptable or reasonable for most participants. One participant perceived that their response to CHM was worth the cost. However, some participants believed that the expense of CHM was high, especially when used in combination with WM. For participants without medical insurance support, such as students, the cost of CHM alone or in combination with WM was high due to long-term use:

> For Chinese herbal medicine, then I used to get also other treatments combined with Chinese herbal medicine, so I feel that the cost-effective, Chinese medicine may have a relatively a good response for the cost, comparing with western medicine. (中药的话，我那个中药主要还配合其他的治疗，所以我感觉，可能西药的，就是性价比来说，中药可能是比较好的性价比). (Participant AU 003 chronic urticaria)

> The impact is not big because [it is] RMB 20 for one pack, one pack for two days, which means RMB 10 for one day. It is acceptable for me. (这个影响不大吧，因为一剂药 20 多块钱，然后分两天喝，一天就是 10 块钱。这个倒能接受). (Participant CHN 009 psoriasis vulgaris)

9.10 Discussion

This study described patients' experiences living with psoriasis vulgaris or chronic urticaria, and their experience using CHM for these two conditions. Participants experienced the typical symptoms of the conditions, such as erythema and scale for psoriasis vulgaris, and wheals and pruritus for chronic urticaria. These symptoms imposed physical and psychological burdens on participants, and significantly affected their QoL.

Key themes

Symptoms such as itching/scratching, flaking/scaling and pain were reported by participants in this study. These symptoms have been reported in a multicentre qualitative study in the US (260). Pariser *et al*. explored patients' experiences living with psoriasis, and found the most bothersome symptoms were itching/scratching, flaking/scaling (non-scalp areas) and skin pain (260). These were reported to have a significant impact on social life. Similar experiences were reported by participants in this study, with low quality sleep due to scratching, skin pain, dealing with scaling, and impact on work and study efficiency, sports, food and clothing selection.

Previous studies suggested that psoriasis affected patients' psychological wellbeing, which included lowered self-esteem, anxiety, sexual dysfunction and depression (18, 19). Another qualitative study showed that emotional impact was the most frequently reported effect (260). The psychological burden was also highlighted by participants with psoriasis vulgaris in this study. The long-term manifestation of disfigured appearance caused psychological conditions, such as depression and anxiety. They were worried about other people's misunderstandings of the contagiousness of psoriasis vulgaris. The comorbidity of disease was another concern for participants.

It has been reported that chronic urticaria results in functional limitation including mobility (17), pain (16, 17), energy (17), sleep (14–17) and mood changes including depression, life stress, social interaction and emotional reactions (14–17). These were also confirmed in this study, with the exception of limitation of mobility, which was rarely mentioned. O'Donnell *et al*. (17) assessed mobility using the Nottingham Health Profile, which asks a series of questions about physical abilities. Over half of the participants had delayed pressure urticaria (DPU). Participants with DPU had greater mobility limitations than those with uncomplicated

chronic urticaria did. However, questions about mobility were not specifically asked during the interview in this study. In addition, it was uncertain whether participants in this study suffered from DPU, as the causes of chronic urticaria were not documented.

This study found that the distress from long-term symptoms and uncertainty about disease progression in participants with psoriasis vulgaris was greater than in participants with chronic urticaria. Participants with both conditions were uncertain about the occurrence and absence of symptoms, and the effects of treatments. These triggered anxiety, dysphoria and desperation about their future. As the symptoms of chronic urticaria came and went rapidly, participants had less of a focus on appearance. They simply felt dysphoric about the frequent occurrence of wheals and pruritus, or in more severe cases, laryngeal oedema. Compared with chronic urticaria, the impact of psoriasis vulgaris on social life was far reaching. The disfigured appearance of people with psoriasis vulgaris might prevent participants from attending social activities. However, participants with chronic urticaria can take medication to relieve symptoms rapidly and continue social activities.

Factors triggering or aggravating their skin conditions also bothered participants' in their daily lives. They had to be careful about potential trigger factors that may cause the occurrence of symptoms. For psoriasis vulgaris, the factors were drinking alcohol or staying up late. One participant described that her menstrual cycle could also exacerbate psoriasis vulgaris. This finding was consistent with previous understandings that various dermatoses, including psoriasis, peak at or around the time of menstruation (261). The risk factors described in clinical guidelines were also confirmed in this study (10, 12, 13). Chronic urticaria could be triggered or aggravated by temperature change, diet, sleep and anxiety. Seafood could trigger or exacerbate both psoriasis vulgaris and chronic urticaria.

Conventional treatment has a rapid effect, but carries a high relapse rate or short-lived effect. However, long-term use of conventional treatments resulted in unsatisfying side effects that made participants lose confidence in conventional treatments. Based on participants' own beliefs and experiences, they sought CHM as alternative. At the mercy of culture and professional education background, participants believed and expected that CHM could improve personal constitution, treat the root (underlying factor) of the disease and reduce relapse rates with fewer side effects. In addition, the motivator of one participant to choose CHM was her interest and fascination with herbs. She enjoyed the CHM treatment experience.

Most participants reported a satisfactory response to CHM. In addition to the improvement of skin symptoms, CHM also regulated the general health of participants. It made participants more energetic, improved their mood and reduced the frequency of the common cold. Moreover, CHM was well tolerated and could reduce relapse rates. CHM did not have a negative impact on participants' menstruation. Rather, it appeared to regulate it. The cost of CHM was acceptable for most participants.

However, a few participants pointed out that it took a long time to achieve improvement using CHM. Participants also found CHM hard to manage, as making CHM decoctions was time-consuming and inconvenient. The most painful thing for some participants was to drink CHM as it was unpalatable and caused nausea in some. CHM also caused gastrointestinal reactions.

Very little research has examined the preferences of patients relating to herbal medicine. One US survey suggested that patients preferred capsules/pills and tinctures due to the ease of administration, taste and time constraints (262). These preferences were echoed by participants in this study. Manufactured CHM products, such as granules, capsules and tablets, were considered an easy option to use. Participants believed that granules could

increase their adherence and guarantee better efficacy since the CHM products were easy to take quickly. Moreover, one participant trusted CHM products that were developed through rigorous assessments of clinical trials instead of prescription by CM practitioner. However, some participants preferred raw herbs or decoction in this study. They had belief or experience of better efficacy with decoctions compared with manufactured CHM products. Similarly, Griffin *et al*. (262) found some participants perceived raw herbs or tinctures to be more potent or concentrated.

Participants in this study also expressed concern about the side effects and cost of CHM for long-term use. These were also mentioned in the study of Griffin *et al*. (262). In addition, participants considered it important to tailor the treatment method to suit participants' responses and expectations. Patients' preferences for treatment should be considered.

Limitations of the Study

Several limitations of this study should be acknowledged. Only one Caucasian who received CHM treatment in Australia was recruited. Other participants were Chinese and received treatments in China. When comparing this study with Griffin *et al*. (262), similarities on the preference of CHM preparation (such as the preference for capsules) were discovered. However, difference was also observed in terms of participants' motivators to choose CHM and preferred preparation types. These might be due to cultural difference between countries. Griffin *et al*. (262) conducted a survey of patients at a community acupuncture clinic in the US. However, most participants in this study were from China and received CHM from hospital outpatient departments in China. While some similarities were observed between preferences in the US and China, it remains uncertain whether the same similarities or differences exist between China and Australia. In addition, participants in China were from one province only (Guangdong/Canton), which may not be representative of the whole of

China. As some participants in this study mentioned, they were influenced by the culture in Canton and preferred CHM treatment. Furthermore, this study only recruited participants who selected CHM and explored their motivators to choose CHM. For participants who chose not to seek CHM as treatment, their reasons for not choosing CHM remain unclear.

Implications for Clinical Practice and Research

This study provided implications for both clinical practice and research. Patients' experiences living with psoriasis vulgaris and chronic urticaria and their expectations for treatment should be taken into consideration when determining treatment strategy. Treatment should not only focus on improving skin symptoms, but also focus on patients' QoL and psychological issues. As one study mentioned, patients' experiences should be taken into consideration in the assessment and treatment of disease (263). The expectation of participants for treatments in this study was to reduce relapse with no side effects and to be easy to access. This expectation should also be considered when formulating the treatment. Further, it is better to inform patients about what to expect with treatment, such as differences in the onset of treatment effect between CHM and WM. For example, many of WM treatments act quickly, while CHM can take longer to achieve clinical changes.

Patients can be informed and educated through multiple sources, such as the internet or patient seminars. It is interesting to note that 34% of participants selected CHM based on personal research or the internet (262). To guarantee better efficacy of CHM, it is important to improve patients' experiences of using CHM, such as preparation type and taste of CHM. Ideally, convenient and palatable CHM products should be developed. This will increase patients' adherence and contribute to an improvement in symptoms.

In addition, it is valuable to explore participants' consideration who choose not to seek CHM as treatment. This can highlight their belief and concern about CHM, which will be helpful to

idenfity the gap of CHM in the management of chronic urticaria and psoriasis vulgaris. Knowing what patients did not like may address some of the reasons why people did not choose CHM. For example, some patients indicated that CHM is not easy to use, due to the taste or time required to prepare the CHM. To an extent, the taste of the herbs can be changed, although practitioners would need to consider whether such changes would reduce the therapeutic effect of the formula. Further, knowing that patients are time-limited may mean that granules are easier for patients, would increase adherence, and may make CHM a more attractive treatment option.

9.11 Conclusion

Patients living with psoriasis vulgaris and chronic urticaria experience physical and psychological burdens in their lives. Patients' experiences and expectations should be considered when formulating CHM treatment. Knowing patients' expectations and real experiences is helpful to communicate with patients about their therapeutic options. The collaboration between patients and practitioners (therapeutic partnership) plays a critical role in clinical decision-making and therapeutic outcomes.

Chapter 10. General Discussion and Conclusions

10.1 Introduction

Chronic urticaria and psoriasis vulgaris are two common chronic skin conditions, which are related to immune dysfunction and triggered by external factors (10–13). Both conditions place considerable health-related burdens on patients, and have ongoing economic effects on individuals and healthcare systems (13–22). For both conditions, WM can provide rapid relief of symptoms. However, challenges remain in relation to unsatisfying side effects and a lack of treatment response for some patients after long-term use (10, 12, 13, 23). CAM has become an option for patients. The use of CAM, including herbal medicine for skin conditions, is increasing (24–26). It is valuable to evaluate and synthesise the evidence on CHM for both conditions, as gaps have been identified.

This project addressed these gaps through a systematic evaluation of the 'whole evidence' from classical literature and comprehensive SRs on modern literature. When translating the evidence about CHM into clinical practice, patients' experiences and expectations of using CHM should be considered. Further, a qualitative study was conducted to explore patients' experiences of living with chronic urticaria and psoriasis vulgaris and using CHM to manage the conditions.

10.2 Summary of Findings

Classical literature research was conducted on the *ZHYD* (*Encyclopaedia of traditional Chinese medicine)*, which is one of the largest digital collections of CM classical books. Among the citations related to urticaria and psoriasis vulgaris in classical literature, the most frequently reported formulae and herbs were identified. *Xiao feng san* 消风散 was the most

commonly used formula for urticaria in the classical books, which is still used in current clinical practice (see Chapter 3). For psoriasis vulgaris, the most frequently reported formula was *Sou feng shun qi wan* 搜风顺气丸, which is not consistent with contemporary textbooks or clinical guidelines (see Chapter 3). Although no similarities were found in formulae used for both conditions, several herbs were used, including *fang feng* 防风, *jing jie* 荆芥, *gan cao* 甘草, *qiang huo* 羌活, *dang gui* 当归 and *chuan xiong* 川芎. These herbs are also recommended in current textbooks or clinical guidelines (see Chapter 3).

Evidence from clinical studies was evaluated through SRs of RCTs following the rigorous method outlined by the *Cochrane handbook* (89). Two SRs on CHM for chronic urticaria showed that CHM alone or as add-on therapy to second-generation antihistamines, improved symptoms of chronic urticaria by 30% or more when compared with second-generation antihistamines. However, these findings were limited by uncertain validity (for example, generalisability of results to the population and variations of the instructions) of outcome measures used in most studies. A few studies reported validated outcomes such as UAS and DLQI, with findings suggesting that CHM was promising in improving symptoms (UAS) and HR-QoL (DLQI) of patients with chronic urticaria. CHM was well tolerated by patients with chronic urticaria. The number of AEs in patients who received CHM was lower than those who used CM and the main AEs were gastrointestinal reactions. It may be effective and safe to use CHM alone or as add-on therapy to second-generation antihistamines in the treatment of chronic urticaria. In addition, the methodological limitations of the included studies should be taken into consideration when interpreting these findings. Future clinical research following appropriate randomisation, allocation and blinding methods with validated outcomes is needed to provide robust evidence.

SRs on CHM for chronic urticaria also identified several commonly evaluated formulae and key herbs. *Yu ping feng san* 玉屏风散, *Dang gui yin zi* 当归饮子 and *Xiao feng san* 消风散 were among the most frequently used formulae in clinical studies. Further, all three formulae are recommended by textbooks and clinical guidelines (see Chapter 3). *Xiao feng san* 消风散 was the most frequently reported formula in classical literature (see Chapter 4). This formula has been evaluated in the SR (Chapter 7) and has a history of use that extends back to the classical literature. *Xiao feng san* 消风散 is also recommended in contemporary clinical textbooks and guidelines. These factors in combination suggest *Xiao feng san* 消风散 can be considered a promising formula in the treatment of chronic urticaria.

Further, *Yu ping feng san* 玉屏风散 and *Dang gui yin zi* 当归饮子 were recommended and evaluated in clinical studies, but were not found in the classical literature. There are several possible reasons why these formulae were not found in classical literature. First, this project may not have identified all the relevant citations related to urticaria in classical literature. A comprehensive search of the *ZHYD* was conducted using eight terms, but other terms may have been used for urticaria in the classical literature that were not used by this project. In addition, the *ZHYD* does not cover all the classical CM books. Second, formulae names may vary while the herb ingredients remain the same. This project based frequency calculations on formula name. Therefore, it is possible that some citations that included the same ingredients as *Yu ping feng san* 玉屏风散 and *Dang gui yin zi* 当归饮子, but were named differently, were not included. Accordingly, these two formulae may have been used in classical literature but were not identified by this project. Third, the judgment criteria used to assess eligibility of citations (see Chapter 4) may have excluded some citations relating to urticaria. So, while *Yu ping feng san* 玉屏风散 and *Dang gui yin zi* 当归饮子 were not identified in

classical literature, these two formulae may be considered in clinical practice based on syndrome differentiation.

The key herbs identified from SRs of chronic urticaria were *fang feng* 防风, *huang qi* 黄芪, *dang gui* 当归, *gan cao* 甘草, *jing jie* 荆芥 and *bai zhu* 白术. These herbs were described in both classical literature and textbooks and clinical guidelines (see Chapters 3 and 4). *Jing jie* 荆芥 and *fang feng* 防风 can disperse external wind to stop itch. *Huang qi* 黄芪 tonifies Lung and Spleen *qi* to secure the exterior. *Bai zhu* 白朮 tonifies Spleen *qi* to assist securing the exterior. *Dang gui* 当归 nourishes Blood and harmonises nutritive level. *Gan cao* 甘草 regulates the Stomach and Spleen, and harmonises all formula ingredients. Chronic urticaria is a condition caused by internal (underlying) and external factors. The internal factor is deficiency of *qi* and Blood, or failure of defensive *qi* in protecting the exterior. It can be triggered by external pathogenic attack, such as wind-heat or wind-cold. When influenced by other factors such as food or emotional disharmony, the disease can develop into other syndromes like dampness in the Stomach and Intestine, *qi* and Blood stagnation and stasis. The frequently used herbs in SRs, which were also described in classical literature, targeted the key pathogenesis of chronic urticaria from a CM perspective.

The most frequently reported herbs and formulae in RCTs of CHM for chronic urticaria were selected for a general review of experimental studies (see Chapters 6 and 7). Herbs *fang feng* 防风, *huang qi* 黄芪, *dang gui* 当归, *gan cao* 甘草, *jing jie* 荆芥 and *bai zhu* 白术 appeared to have anti-inflammatory, anti-allergenic and/or antipruritic actions. *Yu ping feng san* 玉屏风散 (consisting of *fang feng* 防风, *huang qi* 黄芪 and *bai zhu* 白术) and its extract also showed anti-allergic and anti-inflammatory effects *in vitro* and *in vivo*. This explains the

potential mechanism of these herbs and their combinations in the treatment of chronic urticaria.

As previous SRs on psoriasis vulgaris focused on the evaluation of CHM as an intervention (28–31), no reviews were identified that examined the efficacy of a particular herb, formula or product. In addition, *gan cao* 甘草 was used in the treatment of both chronic urticaria and psoriasis vulgaris in classical literature. Moreover, CG for chronic urticaria was also evaluated in this thesis. Therefore, the third SR focused on the add-on effect of CG to conventional therapy for psoriasis vulgaris. CG as add-on therapy to conventional therapy enhanced clinical response in terms of PASI 60 or 90, and did not increase the frequency of AEs for patients with psoriasis vulgaris. However, readers should be cautious when interpreting the findings due to methodological flaws of included studies. The long-term add-on effect was uncertain. More robust evidence evaluating CG is needed, such as a randomised, double-blinded, placebo-controlled design. Experimental evidence indicated that CG had anti-inflammatory and immune-modulating effects.

It should be noted that the herb *gan cao* 甘草 was used for both urticaria and psoriasis vulgaris. *Gan cao* 甘草 was the most frequently used herb in classical literature for chronic urticaria. However, it did not appear in the most frequently used herb list in psoriasis classical literature. In modern clinical evidence, CG with extract from *gan cao* 甘草 as a key constituent has been used in both chronic urticaria and psoriasis. This indicates *gan cao* 甘草 and its extracts can be used in the treatment of both conditions. *Gan cao* 甘草 is often considered to harmonise the ingredients of a formula. Despite this, its actions are more targeted than simply harmonising formulae. *Gan cao* 甘草 also possesses both anti-allergic and anti-inflammatory properties, and CG has anti-inflammatory and immune-modulating effects. These provide inspiration and suggestions for clinical practice and further research

into the actions of *gan cao* 甘草. It is not solely a harmonising ingredient; it also has anti-allergic and anti-inflammatory qualities.

When translating evidence into practice, it is valuable to consider practicalities, such as patients' experiences and expectations of using CHM. The qualitative description method was used to explore patients' experiences living with these two conditions and using CHM. This study interviewed 16 participants in Guangzhou, China and five participants in Melbourne, Australia. The findings suggested that participants living with psoriasis vulgaris or chronic urticaria perceived a bleak future due to their conditions. They reported both physical and psychological burdens due to the typical symptoms of the conditions, which had significant effects on their QoL. Most participants began with conventional treatment, which delivered a rapid onset and short-lived effect. Participants increasingly expected accessible treatments that could reduce relapse rates with no side effects. Based on participants' own beliefs, knowledge and experiences, they sought CHM as treatment. Most participants experienced a satisfactory response to CHM, but found it difficult to manage the traditional decoction. Convenient, palatable CHM products were preferred by most participants.

10.3 Limitations of this Project

Several limitations of this project should be acknowledged. The *ZHYD*, which is a comprehensive collection of a wide range of books from the last 2,000 years, was used to conduct classical literature research. While larger collections of classical CM books exist (such as *Chinese materia medica* 中华本草全书 with over 6,000 classical CM books), the *ZHYD*, covering 1,100 classical CM books, was chosen for this project. As a digitalised collection, the *ZHYD* was easily searchable and accessible, and includes key books considered representative of classical literature. As highlighted previously, terms for both

urticaria and psoriasis vulgaris may exist that were not selected for use in this project. Inclusion of any additional terms may alter the results.

The findings from SRs were limited by the quality of included studies. The methodological flaws of the included studies could not be ignored in all three SRs. The methodology issues relating to the included studies have been highlighted in each SR (see Chapters 6–8). For instance, information regarding blinding in most studies was insufficient, which made the outcome assessment less reliable. A few studies provided a detailed description for the generation of a randomised sequence. However, it was unclear or inappropriate for the remaining studies. Inadequate data on the generation of a randomised sequence might cause potential selection bias. The information of blinding for majority studies was insufficient, which made outcome assessment less reliable (89). In addition, most studies included in SRs on CHM for chronic urticaria employed the outcome ER 30 and SSRI 30 with uncertain validity. These two outcomes were not commonly observed in international studies. The lack of adherence to internationally recognised standards makes their validity uncertain. In addition, very few studies included in these SRs used outcomes related to HR-QoL or relapse rates to assess treatments. The recurrence of symptoms had significant impacts on patients' QoL.

For two SRs (Chapters 6 and 7), the database search was limited to English and Chinese databases. An additional Japanese database was searched for the third SR (see Chapter 8). While the search included nine to 10 databases, searching in additional databases (such as Korean databases that include studies of CM) may provide more evidence on the use of CHM for both conditions. In terms of patient recruitment, most included studies did not specify the subtype of chronic urticaria. It remains uncertain whether CHM is effective for patients with specific subtypes, such as chronic spontaneous urticaria or DPU. In terms of the use of CHM

in the included RCTs, standardised formulae were used for all patients during the trials. This differs from the approach used in clinical practice, where the use of CHM is based on syndrome differentiation. It is unknown how the results from the SRs are applicable to clinical practice.

The limitation of qualitative study was related to geographic and cultural factors. Only one Caucasian who received CHM treatment in Australia was interviewed. Other interviews were conducted among participants who were Chinese and received treatments in China. It remains uncertain whether the same similarities or differences in patients' experience exist between China and Australia. Moreover, participants in China came from one province only, which may not be representative of the whole of China.

10.4 Implications for Clinical Practice

This project provided a comprehensive assessment of the 'whole evidence' for clinical decision-making. Some formulae and herbs identified from classical literature were described in contemporary textbooks and clinical guidelines, and were also shown to be effective in the clinical trials. These formulae or herbs can be used in clinical practice. For instance, *Xiao feng san* 消风散 can be a formula for chronic urticaria. Herbs *fang feng* 防风, *huang qi* 黄芪, *dang gui* 当归, *gan cao* 甘草, *jing jie* 荆芥 and *bai zhu* 白术 for chronic urticaria could be considered as modifications for the basic formula based on syndrome differentiation. *Yu ping feng san* 玉屏风散 and *Dang gui yin zi* 当归饮子 can also be taken into consideration based on syndrome differentiation because they were recommended by textbooks and clinical guidelines. For formulae or herbs not described in classical literature, contemporary guidelines or clinical evidence, practitioners should consider their use based on patient syndrome differentiation and practitioner's experience.

For psoriasis vulgaris, formulae identified from classical literature were not consistent with current textbooks or clinical guidelines. Further, it was uncertain whether these formulae were evaluated in the clinical trials as most formulae in SRs (28–31) were self-designed. Making a judgment about similarity of formulae based on herb ingredients in the absence of a common formula name is difficult and open to criticism. The approach in this study was to use the formula name when checking for consistency of use across different types of evidence. For example, *Tao hong si wu tang* 桃红四物汤 consists of *shu di huang* 熟地黄, *dang gui* 当归, *bai shao* 白芍, *chuan xiong* 川芎, *tao ren* 桃仁 and *hong hua* 红花. Practitioners or investigators may modify the basic formula with *jiang can* 僵蚕 (commonly used for itch) according to individual symptoms or experience. The name of the formula might be changed (for example, the new formula with added *jiang can* 僵蚕 may be named as a self-designed formula), but the core formula remains *Tao hong si wu tang* 桃红四物汤. While consistency was not found in formulae for psoriasis vulgaris, this does not mean that consistency does not exist. However, in the absence of consistency in formulae, consistency was found in herbs. Herbs *fang feng* 防风, *jing jie* 荆芥, *gan cao* 甘草, *dang gui* 当归 and *chuan xiong* 川芎 were among the most frequently found in classical literature, and are also recommended by current textbooks or clinical guidelines (see Chapter 3). These herbs could be considered on an individual basis in clinical practice as modifications for the basic formula. In addition, manufactured CHM products, such as CG, can become an option for both chronic urticaria and psoriasis vulgaris.

Patients experienced both physical and psychological burdens due to chronic urticaria and psoriasis vulgaris. They expected accessible treatments that could reduce relapse rates with no side effects. Patients' experiences and expectations should be considered when formulating CHM treatment. Patient involvement in care could increase patients' adherence

and help achieve satisfactory effects, particularly if patients were prescribed their preferred CHM preparation types. Knowing patients' expectation and real experiences improves communication between patients and practitioners. Treatment processes require better collaboration between patients and practitioners.

10.5 Implications for Further Research

Formulae or herbs identified from classical literature can be potential targets in clinical trials or experimental studies for drug discovery where evidence is lacking. SRs identified weaknesses of included studies, such as methodology flaws and the use of outcomes with uncertain validity. This informs future research in several ways. First, clinical registration or protocol should be available or published before the results are published, which can increase transparency in reporting of clinical trials. No registration or protocols were found for the studies included in this project. Insufficient detail in reporting study methods further adds to the lack of clinical trial transparency.

In addition to following a rigorous standard methodology to conduct clinical studies, public involvement in health research is becoming increasingly common (264, 265). It is defined as when patients and members of the public become involved in the design, conduct and dissemination of research (264–266). This increases the relevance of research and improves research quality, such as identification of research priorities and outcome measures, and acceptability of data collection procedures (264, 265). The findings from qualitative study in this project showed patients expected treatment that can reduce relapse rates and result in fewer side effects after long-term use. The treatment goal and outcomes used in the assessment of treatment effect should focus on patients' expectations. Patients preferred convenient CHM products that were palatable and easy to take. Therefore, granules or capsules can be considered, which could increase patients' adherence. As suggested by

Mullins *et al*. (266), patient-centredness in the design of clinical trials motivated patients to participate or continue participating in clinical trials. Comparison of the efficacy of CHM products and decoction should be conducted to evaluate efficacy and safety to alleviate patients' concerns.

10.6 Conclusion

This project evaluated the evidence from classical literature, clinical studies and patients' experiences of CHM for chronic urticaria and psoriasis vulgaris. Evidence from classical literature suggested the most frequently used formulae and herbs for both conditions in ancient CM works, which can guide contemporary clinical practice and new therapeutic development. SRs of clinical evidence produced through this project suggested that CHM was well tolerated and had promising benefits in improving clinical outcomes. These provided evidence of efficacy and safety for clinical decision-making, CM education and further research. Pharmacological actions of key herbs from the SRs include anti-inflammatory, anti-allergenic, antipruritic and immune-modulating actions. This could partially explain the mechanisms of CHM in the treatment of both conditions. Findings from qualitative interviews suggested that patients suffered both physical and psychological burdens due to the conditions. Based on beliefs and experience, they chose CHM and expected that it could reduce relapse with no side effects and be easy to take. Understanding patients' experiences and expectations can assist with communicating with patients and formulating CHM treatment. This can increase patients' compliance in using CHM and contribute valuable information for future research study design.

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Appendices

Appendix 1 Search Terms for Chronic Urticaria

Search Terms for Chinese Language Databases:

Conditions

荨麻疹 OR 瘾疹 OR 隐疹 OR 风疹块 OR 风团 OR 风疹团

Interventions

中医 OR 中西医 OR 中医疗法 OR 辨病论治 OR 辨证 OR 辨证论治 OR 辨症施治 OR 辩证 OR 汉方 OR 祖国医学 OR 传统医学 OR 传统治疗 OR 传统疗法 OR 替代医学 OR 替代治疗 OR 中国传统医学 OR 民族医药 OR 民族医学 OR 草药 OR 中草药 OR 中药 OR 中药疗法 OR 中西药 OR 传统医药 OR 中成药 OR 植物药 OR 中医治法 OR 治则 OR 中医疗法 OR 熏洗 OR 薰洗 OR 浸洗 OR 药浴 OR 洗浴 OR 外洗 OR 沐足 OR 足浴 OR 浴足 OR 灌肠 OR 热熨 OR 热敷 OR 敷脐 OR 药烘 OR 足疗 OR 雾化 OR 中药外敷 OR 外敷 OR 蒸熏 OR 蒸薰 OR 熏蒸 OR 薰蒸

Study Designs

系统评价 OR meta OR 荟萃分析 OR 系统分析 OR 综述 OR 进展 OR 概况 OR 现状 OR 近况 OR 临床观察 OR 临床评估 OR 临床试验 OR 临床效果 OR 临床研究 OR 疗效 OR 评价研究 OR 前瞻性 OR 随访 OR 对比研究 OR 多中心 OR 随机 OR 对照 OR 病例报告 OR 病例研究 OR 病例分析 OR 病例报道

Search Terms for English Language Databases:

Conditions

Wheal OR hives OR urticaria

Interventions

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 Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Chinese Medicine Herb OR Herbal Medicine OR Herbs

Study Designs

Review articles: Systematic

Randomized Controlled Trial: randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups

Other Studies: cohort studies OR case-control studies OR comparative study OR risk factors OR cohort OR compared OR groups OR case control OR multivariate OR case series

Appendix 2 Search Terms for Psoriasis Vulgaris

Search Terms for Chinese Language Databases:

Conditions

银屑病 OR 白疕 OR 松皮癣 OR 掌跖脓疱病

Interventions

甘草酸 OR 美能 OR 甘草甜素 OR 强力宁 OR 甘毓

Study Designs

临床观察 OR 临床评估 OR 临床试验 OR 临床效果 OR 临床研究 OR 疗效 OR 评价研究 OR 前瞻性 OR 随访 OR 对比研究 OR 多中心 OR 随机 OR 对照 OR 病例报告 OR 病例研究 OR 病例分析 OR 病例报道

Search Terms for English Language Databases:

Conditions

Skin Diseases, Papulosquamous OR Psoriasis OR Psoria* OR Arthritis, Psoriatic OR Pustulosis of Palms and Soles OR Pustulosis Palmaris et Plantaris OR Palmoplantaris Pustulosis OR Pustular Psoriasis of Palms and Soles

Interventions

Glycyrrhizic Acid OR glycyrrhizic acid OR glycyrrhizin OR glycyrrhizinic acid OR glycyrrhizic acid OR licorice OR liquorice OR Stronger Neo-minophagen C OR Compound Glycyrrhizin

Study Designs

Randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR drug therapy OR randomly OR trial OR groups

Search Terms for Japanese Language Database:

Conditions

乾癬 OR 白疕 OR 銀屑病 OR 松皮癬 OR 掌蹠膿疱症

Interventions

グリチルリチン OR グリシルリジン OR 強力ネオミノファーゲンシー OR 强力宁 OR 甘毓

Study Designs

臨床観察 OR 臨床評価 OR 臨床試験 OR 臨床効果 OR 臨床研究 OR 効果 OR 評価研究 OR 前向き研究 OR フォローアップ OR 比較研究 OR 比較試験 OR 多施設 OR ランダム OR 無作為 OR コントロール OR 対照 OR 症例報告 OR 事列研究 OR ケーススタディ OR 症例分析 OR 症例報告

Appendix 3 Examples of Data Extraction Forms

Characteristics

First author; publication year; country; setting	Study design; blinding; number of arms	Treatment duration; total number of treatments; follow-up duration	Stage; severity; duration of condition (mean [SD] or range)	No. of participants randomised/assessed; dropouts	Age (mean (SD) or range); gender (M/F)	Intervention	Comparator

Intervention

First author, publication year	Syndromes	CM principle of treatment	Intervention	Details	Comparator (specify)	Dosage and administration

Outcomes

First author, publication year	Symptom severity	Quality of life	Relapse rate	Adverse events

Appendix 4 Interview Guide

Study ID: _____

Qualitative study: Patient experiences of using CHM for chronic skin conditions

Interview guide

The questions below are examples of questions that may be used to guide interviews with participants. The order of questioning may vary depending on participants' responses, and may be subject to minor revisions throughout the duration of the project.

1. Tell me about your skin condition.
a. When did you first discover you had psoriasis/chronic urticaria?
b. How did you feel when it was diagnosed?
c. What symptoms did you have for your condition?
d. Do you still have psoriasis/chronic urticaria now?
i. (If yes) Is the condition always there or does it come and go?
e. How has having psoriasis/chronic urticaria affected your life?
f. What impact has it had on your physical health?
g. What impact has it had on your sleep and energy levels?
h. What impact has it had on your emotional health?
i. What impact has it had on work or study?
j. What impact has it had on your social life and relationships?
k. What impact has it had on your finances?
l. Do you think that your condition will affect your life in the future?

2. Can you tell me what treatments you have tried for your condition?
a. What sort of results did you get from that/those treatments?
b. What led you to decide to use Chinese medicine?
c. How did you find the Chinese medicine practitioner you saw?

3. Tell me what it was like to use the Chinese herbs.
a. Can you describe the Chinese herbs you received?
b. How often did you have to use them?
c. What sort of changes did you notice when using the Chinese herbs?
d. What sort of impact did the Chinese herbs have on your finances?
e. If you had a friend with the same skin condition, what would you tell them about Chinese herbs?

4. We've covered quite a few topics here, is there anything else you'd like to add?

Demographic data
a. Age
b. Gender
c. Postcode
d. Ethnicity
f. Education
g. Employment

Date of interview
Time of interview

Appendix 5 Participant Information and Consent Form

The Participant Information and Consent Form (PICF)

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

PARTICIPANT INFORMATION

Project Title: *Qualitative study: Patient experiences of using CHM for chronic skin conditions*

Investigators:

Prof. Charlie Xue, BMed, PhD; Registered Chinese medicine practitioner
Head of School of Health Sciences, RMIT University
charlie.xue@rmit.edu.au
9925 7360

Dr. Tony Zhang, BMed, MPH, PhD; Registered Chinese medicine practitioner
Head of Discipline of Chinese Medicine, RMIT University
tony.zhang@rmit.edu.au
9925 7758

Dr. Meaghan Coyle, PhD; Registered Chinese medicine practitioner
Research Fellow, Discipline of Chinese Medicine, RMIT University
meaghan.coyle@rmit.edu.au
9925 7678

Prof. Chuanjian Lu, MD, PhD
Vice-President, Dermatologist, Guangdong Provincial Hospital of Chinese Medicine
Luchuanjian888@vip.sina.com

Mr Jingjie (Jason) Yu, MMed; Registered Chinese medicine practitioner
PhD Candidate, RMIT University
s3472604@student.rmit.edu.au
9925 7678

Dear Sir/Madam,

You are invited to participate in a research project being conducted by RMIT University through the China-Australia International Research Centre for Chinese Medicine. Please read this sheet carefully and be confident that you understand its contents before deciding whether to participate. If you have any questions about the project, please ask one of the investigators.

Who is involved in this research project? Why is it being conducted?

We are looking to explore people's experiences of living with a chronic skin condition who have used CHM to manage the condition. Currently, there is very little information available on this topic, and we think it's important for us to know. We are inviting approximately 40 people who have either psoriasis or chronic urticaria to participate in this study.

This research study is part of Mr Jingjie (Jason) Yu's PhD project. It is being conducted by collaboration between RMIT University and Guangdong Provincial Hospital of Chinese Medicine. The project is being supervised by Prof Charlie Xue, Prof Chuanjian Lu, Dr Tony Zhang, and Dr Meaghan Coyle. The results will be presented in aggregate at conference presentations and journal publication. You will not be identified in any way.

The project has been approved by RMIT College Human Ethics Advisory Network (No. BSEHAPP 29–15 XUE) and funded by RMIT University in conjunction with Guangdong Provincial Hospital of Chinese Medicine.

Why have you been approached?

You have been approached to participate as you have been previously diagnosed with chronic urticaria or psoriasis vulgaris, and consulted Chinese medicine practitioners for treatment. You may have heard about this study through recruitment posters displayed in a clinic or hospital, through contact from the RMIT Teaching Clinic or after enquiring about a clinical trial.

What is the project about? What are the questions being addressed?

This project is a qualitative interview. This project will explore the experiences of people with chronic urticaria (hives) or psoriasis vulgaris in terms of the impact of the condition on their health and life, and their experiences in using CHM. A total of approximately 40 people will be interviewed individually. Each interview will take approximately 30–60 minutes.

If I agree to participate, what will I be required to do?

If you agree to participate in the study, you will be provided with all the details about the study, and any questions will be answered by the research investigator. Once you sign this participant information consent form (PICF), an interview time will be arranged. Interviews can be conducted either at RMIT (RMIT School of Health Sciences Research Hub, Building 201, Level 3) or at your home if more convenient.

You will spend approximately 30–60 minutes participating in this interview. Several questions will be asked by a researcher, which covers the key topics outlined below:

1. Your experiences with the condition in terms of impact on health and daily life.
2. What led you to choose Chinese herbal medicine?
3. What have been your experiences with using Chinese herbal medicine for the condition?

An audio recording of the interview will be made and a second researcher may be present to record additional non-verbal details (such as gestures) of the interview. Interview will be conducted in English or Chinese (Mandarin) according to your preference.

What are the possible risks or disadvantages?

If you participate in this project, there are no perceived risks outside your normal day-to-day activities. Some of the questions may be embarrassing or make you feel uncomfortable. You have the right to decline to answer particular questions, or to withdraw from the study at any time. The information you provide will be confidential, and will not be accessible to anyone outside of the research team.

If you have any concerns about the responses to any of the questions asked or if you find participation in the project distressing, you should contact one of the investigators Dr Tony Zhang as soon as convenient. Dr Tony Zhang will discuss your concerns with you confidentially and suggest appropriate follow-up, if necessary. You may contact the RMIT Ethics committee or GPHCM ethics committee for concerns that you would prefer them handled by someone outside the research team.

What are the benefits associated with participation?

The findings from this project will provide valuable information which may inform clinical practice and guide future research of Chinese herbal medicine for dermatological conditions. This may improve patients' experience using Chinese herbal medicine.

What will happen to the information I provide?

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. Information that you provide will be identifiable. Where possible and appropriate, identifiable information will be replaced with pseudonyms. Identifiable information will be stored on a password-protected computer, or in a locked filing cabinet. Data will be stored for a minimum of seven years from the date of publication.

Only the researchers involved in the study will have access to this information. Any information that you provide can be disclosed only if:

(1) it is to protect you or others from harm
(2) a court order is produced
(3) you provide the researchers with written permission.

You have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree being corrected. You have the right to withdraw from the study, and you may request your identifiable data be disposed of. Once the interviews have been transcribed, any identifiable information will be removed. Up until this point, you are able to request identifiable information be disposed of. This will be undertaken according to institutional policy, where electronic data will be deleted from storage facilities and hard copies of data will be disposed of in confidential waste bins.

Findings from this project will be published in international peer-reviewed journals, and will be presented at national and international conferences. You will not be identified in any publications from the study. The findings will also be included in the PhD thesis of Mr Jingjie (Jason) Yu which, once approved, will be submitted to the RMIT University Research Repository.

What are my rights as a participant?

- The right to withdraw from participation at any time
- The right to request that any recording cease
- The right to have any unprocessed data withdrawn and destroyed, provided it can be reliably identified, and provided that so doing does not increase the risk for the participant
- The right to have any questions answered at any time.

Whom should I contact if I have any questions?

Any study related questions should be directed to Mr. Jingjie (Jason) Yu at 03 9925 7678.

What other issues should I be aware of before deciding whether to participate?

Before deciding you should assess the requirements of the research for face to face interview. Interview will take approximately 30–60 minutes plus travel time. A $20 voucher will be provided to you in appreciation of your time. You should consider if you can commit the time required to complete the study.

Yours sincerely
Investigators:
Prof. Charlie Xue

Dr. Tony Zhang

Dr. Meaghan Coyle

Prof. Chuanjian Lu

Mr Jingjie (Jason) Yu

If you have any concerns about your participation in this project, which you do not wish to discuss with the researchers, then you can contact the Ethics Officer, Research Integrity, Governance and Systems, RMIT University, GPO Box 2476 VIC 3001. Tel: (03) 9925 2251 or email human.ethics@rmit.edu.au

CONSENT TEMPLATE

1. I have had the project explained to me, and I have read the information sheet.

2. I agree to participate in the research project as described.

3. I agree**:**

   ☐ to be interviewed

   ☐ that my voice will be audio recorded

4. I acknowledge that:

   (a) I understand that my participation is voluntary and that I am free to withdraw from the project at any time and to withdraw any identifiable data previously supplied until the point of de-identification.

   (b) The project is for the purpose of research. It may not be of direct benefit to me.

   (c) The privacy of the personal information I provide will be safeguarded and only disclosed where I have consented to the disclosure or as required by law.

   (d) The security of the research data will be protected during and after completion of the study. The overall findings from data collected during the study will be published, and a report of the project outcomes may be presented at a conference. Any information which will identify me will not be used.

Participant's Consent

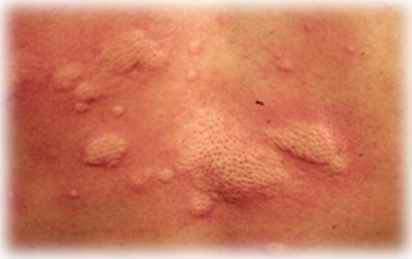
Participant: _____ Date: _____

(Signature)

Appendix 6 Recruitment Poster

RMIT UNIVERSITY

Do you have chronic urticaria or psoriasis? Tell us your experience living with it and using Chinese herbal medicine!



Researchers at RMIT University are conducting a study to explore the experiences of people with chronic urticaria (hives) or psoriasis vulgaris in terms of the impact of the condition on their health and life, and their experiences in using CHM. This project has been approved by the RMIT College Human Ethics Advisory Network (No. BSEHAPP 29-15 XUE).

If you are eligible to participate, you will be interviewed for 30–60 minutes about your experience living with skin disease and using Chinese herbal medicines for it.

Your participation will contribute to valuable information which may inform clinical practice, and guide future research of Chinese herbal medicine for dermatological conditions. This may improve your and other patients' experience of using Chinese herbal medicine.

You will be eligible for this study if you:

- Have previously been diagnosed with chronic urticaria or psoriasis vulgaris
- Used Chinese herbal medicine for the condition
- Are aged from 18-65 years
- Are able to speak and read English

If you or your friends are interested in this project, please contact Dr Jingjie (Jason) Yu or Dr Meaghan Coyle

Ph: 03 9925 7678

Email Meaghan: meaghan.coyle@rmit.edu.au

Experiences with Chinese herbal medicine study
Ph: 03 9925 7678
Email: meaghan.coyle@rmit.edu.au

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Ph: 03 9925 7678
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Appendix 7 Human Research Ethics Approval Letter from RMIT University

RMIT UNIVERSITY

RMIT University

Science Engineering and Health

College Human Ethics Advisory Network (CHEAN)

Plenty Road
Bundoora VIC 3083

PO Box 71
Bundoora VIC 3083
Australia

Tel. +61 3 9925 7096
Fax +61 3 9925 6506
www.rmit.edu.au

16th September 2015

Professor Charlie Xue
Building 201 Level 2, Room 6
School of Health Sciences
RMIT University

Dear Professor Xue

BSEHAPP 29-15 XUE Patient experiences of using Chinese herbal medicine (CHM) for chronic skin conditions: a qualitative study

Thank you for submitting your amended application for review.

I am pleased to inform you that the CHEAN has approved your application for a period of **6 Months** from the date of this letter to **16th March 2016** and your research may now proceed.

The CHEAN would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress.
The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.

Please Note: Annual reports are due on the anniversary of the commencement date for all research projects that have been approved by the CHEAN. Ongoing approval is conditional upon the submission of annual reports failure to provide an annual report may result in Ethics approval being withdrawn.

Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

pp **Dr Falk Scholer**
Deputy Chair, Science Engineering & Health
College Human Ethics Advisory Network

Cc Student Investigator/s: Mr Jingie Yu s3472604 School of Health Sciences RMIT University
Other Investigator/s: Dr Tony Zhang School of Health Sciences RMIT University
Dr Meaghan Coyle School of Health Sciences RMIT University
Prof Chuanjian Lu Guangdong Provincial Hospital of Chinese Medicine

RMIT University

Science Engineering and Health

College Human Ethics Advisory Network (CHEAN)

Plenty Road
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PO Box 71
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www.rmit.edu.au

8th February 2016

Professor Charlie Xue
Building 201 Level 2, Room 6
School of Health Sciences
RMIT University

Dear Professor Xue

BSEHAPP 29-15 XUE Patient experiences of using Chinese herbal medicine (CHM) for chronic skin conditions: a qualitative study

Thank you for requesting a 12 month extension to your Human Research Ethics project titled: ***Patient experiences of using Chinese herbal medicine (CHM) for chronic skin conditions: a qualitative study,*** which was originally approved by Science Engineering and Health CHEAN in September 2015for a period of 6 Months.

I am pleased to inform you that the CHEAN has **approved** your extension request and your Human Research Ethics project is now approved until **16th March 2017**

The CHEAN notes and thanks you for providing all documentation that incorporates these amendments. This documentation will be appended to your file for future reference and your research may now continue.

The committee would like to remind you that:

Annual reports are due on the anniversary of the commencement date for all research projects that have been approved by the CHEAN. Ongoing approval is conditional upon the submission of annual reports failure to provide an annual report may result in Ethics approval being withdrawn.

Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Dr Linda Jones
Chair, Science Engineering & Health
College Human Ethics Advisory Network

Cc Student Investigator/s: Mr Jingie Yu s3472604 School of Health Sciences RMIT University
Other Investigator/s: Dr Tony Zhang School of Health Sciences RMIT University
Dr Meaghan Coyle School of Health Sciences RMIT University
Prof Chuanjian Lu Guangdong Provincial Hospital of Chinese Medicine

Appendix 8 Human Research Ethics Approval Notice from Guangdong Provincial Hospital of Chinese Medicine

伦理审查批件 AF/04-05.2/10.0

广东省中医院伦理委员会

Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine

伦理审查批件

Approval Notice

批件号：广东省中医院伦理委员会B2016-104

审查会议日期	2016年07月21日		
审查会议地点	--		
临床研究批文			
临床研究项目	寻常型银屑病及慢性荨麻疹患者对中药治疗的体验：一项定性研究		
审查文件	1. 伦理审查申请表 2. 研究方案 版本号：001/20160702 3. 访谈提纲 版本号：001/20160702 4. 课题组人员名单，课题负责人履历 5. 招募受试者的材料 版本号：001/20160702 6. 向受试者提供的知情同意书 版本号：001/20160702 7. 所有以前其他伦理委员会或管理机构对申请研究项目的重要决定		
申办者	广东省中医院与澳大利亚皇家墨尔本理工大学		
临床研究单位	广东省中医院		
主要研究者	卢传坚		
伦理审查方式	快速审查		
参会委员	邓丽丽、夏萍		
审查意见	根据国家食品药品监督管理局《药物临床试验质量管理规范》、《药物临床试验伦理审查工作指导原则》，卫生部《涉及人的生物医学研究伦理审查办法》，国家中医药管理局《中医药临床研究伦理审查平台建设规范》，以及世界医学会《赫尔辛基宣言》和国际医学科学组织委员会《人体生物医学研究国际道德指南》的伦理原则，经本伦理委员会审查，同意按照上述临床研究方案和上述已通过审查的文件进行寻常型银屑病及慢性荨麻疹患者对中药治疗的体验：一项定性研究临床研究。		
伦理委员会声明	本批件将在各中心机构及其伦理委员会备案。如果对方案在本机构的可行性（包括研究者的资格与经验、设备与条件等）有不同意见，请及时与本伦理委员会联系。 如项目暂停/提前终止/完成临床研究，请及时通知伦理委员会。如发生严重不良事件以及影响研究风险受益比的非预期不良事件，应及时报告本伦理委员会。如临床研究方案、知情同意书的任何修改，主要研究者更换，应及时通知伦理委员会，重新审查，获得批准后执行。发现影响受试者参加研究意愿的违反方案情况应及时报告。请在本批件失效日期前1个月提交研究进度/结题报告，以便对该项目进行跟踪审查。		
批件有效期	自2016年07月22日起 至2018年07月22日止	跟踪审查频率 预计审查日期	12个月 2017年07月22日
联系电话	020-81887233转35943，联系人：李晓彦		
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	广东省中医院伦理委员会（盖章） 日期：2016年07月22日		

Appendix 9 List of Herbs Used in This Thesis

***Pinyin* Name**	**Simplified Chinese Characters**	**Scientific Name**	**Pharmaceutical Name**
Ai ye	艾叶	*Artemisia argyi* Lévl. et Vant.	Artemisiae Argyi Folium
Ba ji tian	巴戟天	*Morinda officinalis* How	Morindae Officinalis Radix
Bai bian dou	白扁豆	*Dolichos lablab* L.	Lablab Semen Album
Bai bu	百部	1. *Stemona sessilifolia* (Miq.) Miq. 2. *Stemona japonica* (Bl.) Miq. 3. *Stemona tuberosa* Lour.	Stemonae Radix
Bai fan	白矾	*Potassium aluminium* sulfate	Alumen
Bai hua she she cao	白花蛇舌草	*Hedyotis diffusa* Willd.	Hedyotis diffusae Herba

Bai jie zi	白芥子	1. *Sinapis alba* L. 2. *Brassica juncea* (L.) Czern. et Coss.	Sinapis Semen
Bai lian	白蔹	*Ampelopsis japonica* (Thunb.) Makino	Ampelopsis Radix
Bai shao	白芍	*Paeonia lactiflora* Pall.	Paeoniae Radix Alba
Bai xian pi	白鲜皮	*Dictamnus dasycarpus* Turcz.	Dictamni Cortex
Bai zhi	白芷	1. *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f. 2. *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f. var. *formosana* (Boiss.) Shan et Yuan	Angelicae Dahuricae Radix
Bai zhu	白朮	*Atractylodes macrocephala* Koidz.	Atractylodis Macrocephalae Rhizoma

Ban xia	半夏	*Pinellia ternata* (Thunb.) Breit.	Pinelliae Rhizoma
Bi ma zi	蓖麻子	*Ricinus communis* L.	Ricini Semen
Bing lang	槟榔	*Areca catechu* L.	Arecae Semen
Bo he	薄荷	*Mentha haplocalyx* Briq.	Menthae Haplocalycis Herba
Cang er zi	苍耳子	*Xanthium sibiricum* Patr.	Xanthii Fructus
Cang zhu	苍术	1. *Atractylodes lancea* (Thunb.) DC. 2. *Atractylodes chinensis* (DC.) Koidz.	Atractylodis Rhizoma
Cao wu	草乌	*Aconitum kusnezoffii* Reichb.	Aconiti Kusnezoffii Radix
Cao wu tou	草乌头	*Aconitum kusnezoffii* Reichb.	Aconiti Kusnezoffii Radix
Cha	茶	Camellia sinensis [Syn. Thea sinensis]	NA

Chai hu	柴胡	1. *Bupleurum chinense* DC. 2. *Bupleurum scorzonerifolium* Willd.	Bupleuri Radix
Chan tui	蝉蜕	*Cryptotympana pustulata* Fabricius	Cicadae Periostracum
Che qian zi	车前子	1. *Plantago asiatica* L. 2. *Plantago depressa* Willd.	Plantaginis Semen
Chen pi	陈皮	*Citrus reticulata* Blanco	Citri Reticulatae Pericarpium
Chi shao	赤芍	1. *Paeonia lactiflora* Pall. 2. *Paeonia veitchii* Lynch	Paeoniae Radix Rubra
Chi xiao dou	赤小豆	1. *Vigna umbellata* Ohwi et Ohashi 2. *Vigna angularis* Ohwi et Ohashi	Vignae Semen

Chong wei zi	茺蔚子	*Leonurus japonicus* Houtt.	Leonuri Fructus
Chuan xiong	川芎	*Ligusticum chuanxiong* Hort.	Chuanxiong Rhizoma
Chun hua hu zhi zi	春花胡枝子	*Lespedeza dunnii* Schindle	Lespedezae dunnii herba
Ci ji li	刺蒺藜	*Tribulus terrestris* L.	Tribuli Fructus
Cu	醋	Vinegar	NA
Da feng zi	大风子	*Hydnocarpus anthelmintica* Pierre	NA
Da fu pi	大腹皮	*Areca catechu* L.	Arecae Pericarprium
Da huang	大黄	1. *Rheum palmatum* L. 2. *Rheum tanguticum* Maxim. ex Balf. 3. *Rheum officinale* Baill.	Rhei Radix et Rhizoma
Da qing yan	大青盐	Sodium chloride	Halitum
Da qing ye	大青叶	*Isatis indigotica* Fort	Isatidis Folium

Da zao	大枣	*Ziziphus jujuba* Mill.	Jujubae Fructus
Da zao jiao	大皂角	*Gleditsia sinensis* Lam.	Gleditsiae Sinensis Fructus
Dan shen	丹参	*Salvia miltiorrhiza* Bge.	Salviae Miltiorrhizae Radix et Rhizoma
Dan zhu ye	淡竹叶	*Lophatherum gracile* Brongn.	Lophatheri Herba
Dang gui	当归	*Angelica sinensis* (Oliv.) Diels	Angelicae Sinensis Radix
Dang shen	党参	1. *Codonopsis pilosula* (Franch.) Nannf. 2. *Codonopsis pilosula* Nannf. var. *modesta* (Nannf.) L. T. Shen 3. *Codonopsis tangshen* Oliv.	Codonopsis Radix
Di fu zi	地肤子	*Kochia scoparia* (L.) Schrad.	Kochiae Fructus

Di gu pi	地骨皮	1. *Lycium chinense* Mill. 2. *Lycium barbarum* L.	Lycii Cortex
Di huang	地黄	*Rehmannia glutinosa* Libosch.	Rehmanniae Radix
Di long	地龙	1. *Pheretima aspergillum* (E. Perrier) 2. *Pheretima vulgaris* Chen 3. *Pheretima guillelmi* (Michaelsen) 4. *Pheretima pectinifera* Michaelsen	Pheretima
Diao yang chen	吊扬尘	*Buddleja lindleyana* Fort.	NA
Du huo	独活	*Angelica pubescens* Maxim. f. *biserrata* Shan et Yuan	Angelicae Pubescentis Radix

Duan shi gao	煅石膏	Hydrated calcium sulfate	Gypsum Ustum
Fa ban xia	法半夏	*Pinellia ternata* (Thunb.) Breit.	Pinelliae Rhizoma Praeparatum
Fang feng	防风	*Saposhnikovia divaricata* (Turcz.) Schischk.	Saposhnikoviae Radix
Fang ji	防己	*Stephania tetrandra* S. Moore	Stephaniae Tetrandrae Radix
Feng mi	蜂蜜	1. *Apis cerana* Fabricius 2. *Apis mellifera* Linnaeus.	Mel
Fu ling	茯苓	*Poria cocos* (Schw.) Wolf	Poria
Fu ling pi	茯苓皮	*Poria cocos* (Schw.) Wolf	Poriae Cutis
Fu ping	浮萍	*Spirodela polyrrhiza* (L.) Schleid.	Spirodelae Herba
Fu zi	附子	*Aconitum carmichaelii* Debx.	Aconiti Radix Lateralis Praeparata

Gan cao	甘草	1. *Glycyrrhiza uralensis* Fisch. 2. *Glycyrrhiza inflata* Bat. 3. *Glycyrrhiza glabra* L.	Glycyrrhizae Radix et Rhizoma
Gan song	甘松	*Nardostachys jatamansi* DC.	Nardostachyos Radix et Rhizoma
Gao ben	藁本	1. *Ligusticum sinense* Oliv. 2. *Ligusticum jeholense* Nakai et Kitag.	Ligustici Rhizoma et Radix
Ge gen	葛根	*Pueraria lobata* (Willd.) Ohwi	Puerariae Lobatae Radix
Gou qi zi	枸杞子	*Lycium barbarum* L.	Lycii Fructus

Gou teng	钩藤	1. *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. 2. *Uncaria macrophylla* Wall. 3. *Uncaria hirsuta* Havil. 4. *Uncaria sinensis* (Oliv.) Havil. 5. *Uncaria sessilifructus* Roxb.	Uncariae Ramulus cum Uncis
Gui zhi	桂枝	*Cinnamomum cassia* Presl	Cinnamomi Ramulus
He huan pi	合欢皮	*Albizia julibrissin* Durazz.	Albiziae Cortex
He shi	鹤虱	*Carpesium abrotanoides* L.	Carpesii Fructus
He shou wu	何首乌	*Polygonum multiflorum* Thunb.	Polygoni Multiflori Radix

Hong hua	红花	*Carthamus tinctorius* L.	Carthami Flos
Hong huo ma	红活麻	*Urtica amgustifolia* Fisch. Ex Hornem.	NA
Hu ma ren	胡麻仁	*Lespedeza dunnii* Schindle	Lespedezae dunnii herba
Hua jiao	花椒	1. *Zanthoxylum schinifolium* Sieb. et Zucc. 2. *Zanthoxylum bungeanum* Maxim.	Zanthoxyli Pericarpium
Hua pi	桦皮	*Betula luminifera*	NA
Hua shi	滑石	Hydrated magnesium silicate	Talcum
Huai bai pi	槐白皮	*Sophora japonica* L.	NA
Huai hua	槐花	*Sophora japonica* L.	Sophorae Flos
Huai mi	槐米	*Sophora japonica* L.	Sophorae Flos
Huang bai	黄柏	*Phellodendron chinense* Schneid.	Phellodendri Chinensis Cortex

Huang bo	黄柏	*Phellodendron chinense* Schneid.	Phellodendri Chinensis Cortex
Huang la	黄蜡	NA	NA
Huang lian	黄连	1. *Coptis chinensis* Franch. 2. *Coptis deltoidea* C. Y. Cheng et Hsiao 3. *Coptis teeta* Wall.	Coptidis Rhizoma
Huang qi	黄芪	1. *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao 2. *Astragalus membranaceus* (Fisch.) Bge.	Astragali Radix

Huang qin	黄芩	*Scutellaria baicalensis* Georgi	Scutellariae Radix
Huo ma cao	火麻草	*Urtica amgustifolia* Fisch. Ex Hornem.	NA
Huo xiang	藿香	1. *Pogostemon cablin* (Blanco) Benth. 2. *Agastache rugosa* (Fisch. & Mey.) O. Ktze.	Pogostemonis/Agastaches Herba
Ji ji	及己	*Chloranthus serratus*	NA
Ji li	蒺藜	*Tribulus terrestris* L.	Tribuli Fructus
Ji xue teng	鸡血藤	*Spatholobus suberectus* Dunn	Spatholobi Caulis
Jiang can	僵蚕	1. *Bombyx mori* Linnaeus. 2. *Beauveria bassiana* (Bals.) Vuillant	Bombyx Batryticatus

Jiao hong	椒红	1. *Zanthoxylum schinifolium* Sieb. et Zucc. 2. *Zanthoxylum bungeanum* Maxim.	Zanthoxyli Pericarpium
Jie geng	桔梗	*Platycodon grandiflorum* (Jacq.) A. DC.	Platycodonis Radix
Jie zi	芥子	1. *Sinapis alba* L. 2. *Brassica juncea* (L.) Czern. et Coss.	Sinapis Semen
Jin yin hua	金银花	*Lonicera japonica* Thunb.	Lonicerae Japonicae Flos
Jing da ji	京大戟	*Euphorbia pekinensis* Rupr.	Euphorbiae Pekinensis Radix
Jing jie	荆芥	*Schizonepeta tenuifolia* Briq.	Schizonepetae Herba
Jing tian	景天	*Hylotelephium erythrostictum* (Miq.) H. Ohba	NA
Jiu	酒	Liquor	NA

Ju hua	菊花	*Chrysanthemum morifolium* Ramat.	Chrysanthemi Flos
Ku shen	苦参	*Sophora flavescens* Ait.	Sophorae Flavescentis Radix
Ku xing ren	苦杏仁	1. *Prunus armeniaca* L. var. *ansu* Maxim. 2. *Prunus sibirica* L. 3. *Prunus mandshurica* (Maxim.) Koehne 4. *Prunus armeniaca* L.	Armeniacae Semen Amarum
Lang ya cao	狼牙草	Indigofera pseudotinctoria Mats.	NA
Lian qiao	连翘	*Forsythia suspensa* (Thunb.) Vahl	Forsythiae Fructus
Ling yang jiao	羚羊角	*Saiga tatarica* Linnaeus	Saigae Tataricae Cornu
Liu huang	硫黄	Sulfur	Sulfur
Liu zhi	柳枝	Salix babylonica	NA

Long gu	龙骨	Fossilised bone - various species	Fossilia Ossis Mastodi (Draconis Os)[a,b]
Lu jiao jiao	鹿角胶	1. *Cervus elaphus* Linnaeus 2. *Cervus nippon*Temminck	Cervi Cornus Colla
Lu jiao shuang	鹿角霜	1. *Cervus elaphus* Linnaeus 2. *Cervus nippon*Temminck	Cervi Cornu Degelatinatum
Ma chi xian	马齿苋	*Portulaca oleracea* L.	Portulacae Herba
Ma huang	麻黄	1. *Ephedra sinica* Stapf 2. *Ephedra equisetina* Bge. 3. *Ephedra intermedia* Schrenk et C.A. Mey.	Ephedrae Herba
Mai dong	麦冬	*Ophiopogon japonicus* (L.f) Ker-Gawl.	Ophiopogonis Radix

Mai men	麦门冬	*Ophiopogon japonicus* (L.f) Ker-Gawl.	Ophiopogonis Radix
Man jing zi	蔓荆子	1. *Vitex trifolia* L. var. *simplicifolia* Cham. 2. *Vitex trifolia* L.	Viticis Fructus
Mang cao	莽草	*Illicium lanceolatum* A.C. Smith.	NA
Man shan hong	满山红	*Rhododendron dauricum* L.	Rhododendri Daurici Folium
Mang xiao	芒硝	Hydrated sodium sulfate	Natrii Sulfas
Mu bie zi	木鳖子	*Momordica cochinchinensis* (Lour.) Spreng.	Momordicae Semen
Mu dan pi	牡丹皮	*Paeonia suffruticosa* Andr.	Moutan Cortex

Mu li	牡蛎	1. *Ostrea gigas* Thunberg 2. *Ostrea talienwhanensis* Crosse 3. *Ostrea rivularis* Gould	Ostreae Concha
Mu tong	木通	1. *Akebia quinata* (Thunb.) Decne. 2. *Akebia trifoliata* (Thunb.) Koidz. 3. *Akebia trifoliata* (Thunb.) Koidz. var. *australis* (Diels) Rehd.	Akebiae Caulis
Mu xiang	木香	*Aucklandia lappa* Decne.	Aucklandiae Radix
Niu bang zi	牛蒡子	*Arctium lappa* L.	Arctii Fructus
Niu li zi bing gen	牛李子并根	*Rhamnus davurica*	NA
Niu xi	牛膝	*Achyranthes bidentata* Bl.	Achyranthis Bidentatae Radix

Nü zhen zi	女贞子	*Ligustrum lucidum* Ait.	Ligustri Lucidi Fructus
Pao jiang	炮姜	*Zingiber officinale* Rosc.	Zingiberis Rhizoma Praeparatum
Qian hu	前胡	*Peucedanum praeruptorum* Dunn	Peucedani Radix
Qian li guang	千里光	*Senecio scandens* Buch.-Ham.	Senecionis Scandentis Herba
Qiang huo	羌活	1. *Notopterygium incisum* Ting ex H. T. Chang 2. *Notopterygium franchetii* H. de Boiss.	Notopterygii Rhizoma et Radix
Qiang wei gen	蔷薇根	*Rosa multiflora*	NA

Qin jiao	秦艽	1. *Gentiana macrophylla* Pall. 2. *Gentiana straminea* Maxim. 3. *Gentiana crassicaulis* Duthie ex Burk. 4. *Gentiana dahurica* Fisch.	Gentianae Macrophyllae Radix
Qing dai	青黛	1. *Baphicacanthus cusia* (Nees) Bremek. 2. *Polygonum tinctorium* Ait. 3. *Isatis indigotica* Fort.	Indigo Naturalis
Qing fen	轻粉	Mercurous chloride	Calomelas
Qing xiang ye	青葙叶	*Celosia argentea*	NA
Quan xie	全蝎	*Buthus martensii* Karsch	Scorpio

Ren gong niu huang	人工牛黄	N/A	Bovis Calculus Artifactus
Ren shen	人参	*Panax ginseng* C. A. Mey.	Ginseng Radix et Rhizoma
Rou cong rong	肉苁蓉	1. *Cistanche deserticola* Y. C. Ma 2. *Cistanche tubulosa* (Schrenk) Wight	Cistanches Herba
Rou gui	肉桂	*Cinnamomum cassia* Presl	Cinnamomi Cortex
San qi	三七	*Panax notoginseng* (Burk.) F.H.Chen	Notoginseng Radix et Rhizoma
Sang bai pi	桑白皮	*Morus alba* L.	Mori Cortex
Sang ji sheng	桑寄生	*Taxillus chinensis* (DC.) Danser	Taxilli Herba
Sang ye	桑叶	*Morus alba* L.	Mori Folium
Shan yao	山药	*Dioscorea opposita* Thunb.	Dioscoreae Rhizoma

Shan zha	山楂	1. *Crataegus pinnatifida* Bge. var. *major* N.E. Br. 2. *Crataegus pinnatifida* Bge.	Crataegi Fructus
Shan zhu yu	山茱萸	*Cornus officinalis* Sieb. et Zucc.	Corni Fructus
She chuang zi	蛇床子	*Cnidium monnieri* (L.) Cuss.	Cnidii Fructus
She dan zhi	蛇胆汁	Snake bile	NA
She xian cao	蛇衔草	*Potentilla kleiniana*	NA
Sheng jiang	生姜	*Zingiber officinale* Rosc.	Zingiberis Rhizoma Recens
Sheng ma	升麻	1. *Cimicifuga heracleifolia* Kom. 2. *Cimicifuga dahurica* (Turcz.) Maxim 3. *Cimicifuga foetida* L.	Cimicifugae Rhizoma

Shi chang pu	石菖蒲	*Acorus tatarinowii* Schott	Acori Tatarinowii Rhizoma
Shi gao	石膏	Hydrated calcium sulfate	Gypsum Fibrosum
Shi hu	石斛	1. *Dendrobium nobile* Lindl. 2. *Dendrobium chysotoxum* Lindl. 3. *Dendrobium fimbriatum* Hook.	Dendrobii Caulis
Shou wu teng	首乌藤	*Polygonum multiflorum* Thunb.	Polygoni Multiflori Caulis
Shu di huang	熟地黄	*Rehmannia glutinosa* Libosch.	Rehmanniae Radix Praeparata
Shu fu pian	熟附片	*Aconitum carmichaelii* Debx.	Aconiti Radix Lateralis Praeparata
Shui niu jiao	水牛角	*Bubalus bubalis* Linnaeus	Bubali Cornu
Shuo diao	蒴藿	*Sambucus javanica* Reinw.	NA

Tao ren	桃仁	1. *Prunus persica* (L.) Batsch 2. *Prunus davidiana* (Carr.) Franch.	Persicae Semen
Tao zhi	桃枝	*Prunus persica* (L.) Batsch	Persicae Ramulus
Tian ma	天麻	*Gastrodia elata* Bl.	Gastrodiae Rhizoma
Tian nan xing	天南星	1. *Arisaema erubescens* (Wall.) Schott 2. *Arisaema heterophyllum* Bl. 3. *Arisaema amurense* Maxim.	Arisaematis Rhizoma
Tian qi	田七	*Panax notoginseng* (Burk.) F.H.Chen	Notoginseng Radix et Rhizoma
Tu fu ling	土茯苓	*Smilax glabra* Roxb.	Smilacis Glabrae Rhizoma

Tu si zi	菟丝子	1. *Cuscuta australis* R. Br. 2. *Cuscuta chinensis* Lam.	Cuscutae Semen
Wei ling xian	威灵仙	1. *Clematis chinensis* Osbeck 2. *Clematis hexapetala* Pall. 3. *Clematis manshurica* Rupr.	Clematidis Radix et Rhizoma
Wu gong	蜈蚣	*Scolopendra subspinipes mutilans* L. Koch	Scolopendra
Wu mei	乌梅	*Prunus mume* (Sieb.) Sieb. et Zucc.	Mume Fructus
Wu shao she	乌梢蛇	*Zaocys dhumnades* (Cantor)	Zaocys
Wu wei zi	五味子	*Schisandra chinensis* (Turcz.) Baill.	Schisandrae Chinensis Fructus
Xi he liu	西河柳	*Tamarix chinensis* Lour.	Tamaricis Cacumen

Xi xin	细辛	1. *Asarum heterotropoides* Fr. Schmidt var. *mandshuricum* (Maxim) Kitag. 2. *Asarum sieboldii* Miq. var. *seoulense* Nakai 3. *Asarum sieboldii* Miq.	Asari Radix et Rhizoma
Xiao hong shen	小红参	*Rubia yunnanensis*	NA
Xiong huang	雄黄	Arsenic disulfide	Realgar
Xu chang qing	徐长卿	*Cynanchum paniculatum* (Bge.) Kitag.	Cynanchi Paniculati Radix et Rhizoma
Xuan shen	玄参	*Scrophularia ningpoensis* Hemsl.	Scrophulariae Radix
Yang ti teng	羊蹄藤	Bauhinia championi	NA
Ye ge	野葛	*Pueraria lobata* (Willd.) Ohwi	Puerariae Lobatae Radix

Ye jiao teng	夜交藤	*Polygonum multiflorum* Thunb.	Polygoni Multiflori Caulis
Yi yi ren	薏苡仁	*Coix lacryma-jobi* L. var. *mayuen* (Roman.) Stapf	Coicis Semen
Yin chai hu	银柴胡	*Stellaria dichotoma* L. var. *lanceolata* Bge.	Stellariae Radix
Yin chen	茵陈	1. *Artemisia scoparia* Waldst. et Kit. 2. *Artemisia capillaris* Thunb.	Artemisiae Scopariae Herba
Yin yu	茵芋	*Skimmia reevesiana* Fortune.	NA
Yu li ren	郁李仁	1. *Prunus humilis* Bge. 2. *Prunus japonica* Thunb. 3. *Prunus pedunculata* Maxim.	Pruni Semen
Yu zhu	玉竹	*Polygonatum odoratum* (Mill.) Druce	Polygonati Odorati Rhizoma

Yuan hua	芫花	*Daphne genkwa* Sieb. et Zucc.	Genkwa Flos
Yuan zhi	远志	1. *Polygala tenuifolia* Willd. 2. *Polygala sibirica* L.	Polygalae Radix
Zao jiao	皂角	*Gleditsia sinensis* Lam.	Gleditsiae Sinensis Fructus
Zhang nao	樟脑	*Cinnamomum camphora* (L.) Presl.	Camphora[a,b]
Zhi gan cao	炙甘草	1. *Glycyrrhiza uralensis* Fish. 2. *Glycyrrhiza inflata* Bat. 3. *Glycyrrhiza glabra* L.	Glycyrrhizae Radix et Rhizoma Praeparata cum Melle
Zhi he shou wu	制何首乌	*Polygonum multiflorum* Thunb.	Polygoni Multiflori Radix Praeparata
Zhi mu	知母	*Anemarrhena asphodeloides* Bge.	Anemarrhenae Rhizoma

Zhi qiao	枳壳	*Citrus aurantium L*.	Aurantii Fructus
Zhi shi	枳实	1. *Citrus aurantium* L. 2. *Citrus sinensis* Osbeck	Aurantii Fructus Immaturus
Zhi zhu hua	踯躅花	*Rhododendron dauricum* L.	Rhododendri Daurici Folium
Zhi zi	栀子	*Gardenia jasminoides* Ellis	Gardeniae Fructus
Zhu ling	猪苓	*Polyporus umbellatus* (Pers.) Fires	Polyporus
Zhu sha	朱砂	Mercuric sulfide	Cinnabaris
Zhu shen	猪肾	Pig's kidney	NA
Zhu zhi	猪脂	Lard	NA
Zi bei fu ping	紫背浮萍	*Spirodela polyrrhiza* (L.) Schleid.	Spirodelae Herba
Zi cao	紫草	1. *Arnebia euchroma* (Royle) Johnst. 2. *Arnebia guttata* Bunge	Arnebiae Radix

Zi hua di ding	紫花地丁	*Viola yedoensis* Makino	Violae Herba
Zui yu cao	醉鱼草	*Buddleja lindleyana Fort.*	NA

NA Not available