HERBAL MEDICINES AND PHARMACY

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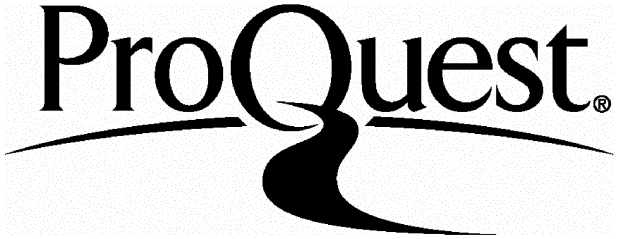

This thesis is dedicated to my wonderful husband Mark, without whose support this research would probably have remained incomplete, and to my parents for their continual encouragement during many years of academic pursuit.

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LIST OF ABBREVIATIONS

ASA	Advertising Standards Authority
BHMA	British Herbal Medicine Association
BMA	British Medical Association
BPH	Benign Prostatic Hypertrophy
CPMP	Committee on Proprietary Medicinal Products
DNA	Deoxyribonucleic Acid
DS	Dietary Supplement
EC	European Community
EMEA	European Medicines Evaluation Agency
ESCOP	European Scientific Co-operative on Phytotherapy
FDA	Food and Drugs Administration
GA	Gamolenic Acid
GP	General Practitioner
GSL	General Sales List
HMWP	High Molecular Weight Polysaccharide
LA	Linolenic Acid
MA	Medicines Act
MAFF	Ministry of Agriculture, Fisheries and Food
MAL	Medicines Act Leaflet
MCA	Medicines Control Agency
MS	Member State
MTU	Medical Toxicology Unit
NDGA	Nordihydroguaiaretic Acid
NHS	National Health Service
PAF	Platelet Aggregating Factor
Ph.Eur.	European Pharmacopoeia
POM	Prescription Only Medicine

SI	Statutory Instrument
SJS	Steven's Johnson Syndrome
SPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
VOD	Veno-Occlusive Disease
WHO	World Health Organisation

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ABSTRACT

In addition to orthodox Western medicine, a plethora of complementary therapies are available in the UK and these have been steadily gaining in popularity since the 1970's. The key areas in which pharmacists are becoming increasingly involved with complementary therapies are in the sale and supply of homoeopathic products, healthfoods and nutritional supplements, and herbal products.

The growing involvement of pharmacists in the supply of herbal medicines is paralleled by a requirement to provide professional advice on the use of these products. As with all medicines, pharmacists should be responsible for supplying herbal medicines of reliable quality, safety and efficacy, and be able to advise patients on such aspects as potential adverse reactions and drug interactions. If pharmacists are to be able to provide professional advice to customers on herbal medicines, then access to reliable information sources is required. However, few pharmacy undergraduate courses provide training on herbal remedies, and the usual reference sources used by pharmacists contain either no or little reference to herbal medicines.

In the present work, European herbs commonly sold through pharmacies have been identified by visiting pharmacies in and around the London area, by reference to popular health magazines and to the Chemist and Druggist listing, and by contact with herbal product manufacturers. Details were obtained for 623 different products from 37 manufacturers, involving some 200 herbal ingredients of which 141 were chosen for subsequent study.

The information sources utilised in the data collation for the 141 identified herbs are listed and represent pharmacopoeias, scientific and non-scientific sources, primary and secondary literature, and on-line databases. It was determined that pharmacists require clinically-orientated information on herbal remedies. Monographs produced for the 141

herbs therefore include headings such as pharmacological actions, side-effects and toxicity, and contra-indications and warnings.

The present work also discusses medicines legislation for herbal remedies, including a historical account of UK legislation and an explanation of the current status of herbal remedies within European legislation. Issues specific to the quality, safety and efficacy assessment of herbal medicines are also discussed. A number of tables and appendixes are included detailing, for example, potential drug/herb interactions, herbs best avoided during pregnancy, and herbs with specific pharmacological actions and constituent types.

Finally, a number of recommendations are made regarding the supply of herbal remedies by pharmacists.

The present work resulted in a reference source entitled "Herbal Medicines - A Guide for Healthcare Professionals", published by the Pharmaceutical Press in January 1996.

1. INTRODUCTION

1.1 Healthcare Systems

In all societies a variety of healthcare options are available. This multi-system environment, known as healthcare pluralism, can be identified in both industrialised and developing countries (Helman, 1994; Sharma, 1992). It has been recognised that any system of healthcare has two inter-related aspects, a cultural aspect and a social aspect. The influence of these two aspects will differ depending on the nature of the healthcare system and the society in which it operates. In general, healthcare systems can be divided into three sectors, professional, folk and popular (Helman, 1994). The professional sector consists of legally sanctioned healing professions such as Western scientific medicine. In some countries, such as China and India, the professional sector may consist of Western scientific medicine alongside an indigenous form of healthcare. Today, the professional sector includes physicians and the various recognised para-medical professions such as nurses, pharmacists, midwives, opticians, dentists and physiotherapists. The folk sector represents individuals who specialise in forms of healing that are either sacred or secular, or a mixture of the two. Traditionally folk healers have existed in all societies and range from secular experts such as bone-setters, midwives, tooth extractors, and herbalists, to spiritual healers and clairvoyants (Helman, 1994). The status of folk healers varies dramatically between societies, but is generally greater in developing countries where the professional sector may either be less prevalent or absent altogether. However, it is within the popular sector that an estimated 70-90% of healthcare takes place, both in Western and non-Western societies (Helman, 1994). The popular sector represents all the various non-professional, non-specialist therapeutic options that individuals utilise within their society. These options include, for example, self-treatment or self-medication, seeking advice from family members, friends or self-help groups, or consulting another layperson with particular experience of a disorder. The type of healthcare pursued within the popular sector will be directly affected by cultural traditions within a particular society.

Despite the general conclusion that it is desirable for all societies to have access to modern Western scientific medicine, the majority of the world's population depend on traditional systems of medicine for their healthcare (Anon, 1978a). In 1979 the World Health Organisation (WHO) issued a declaration of "Health for All by the Year 2000", which aimed to provide affordable worldwide primary healthcare based on Western-style methods (Anon, 1979 & 1981). The difficulties subsequently encountered in achieving this aim underlined the importance of traditional methods of healthcare in developing countries and the need for these methods to be developed alongside Western-style procedures. This concurs with the recommendations of a 1978 WHO report which encouraged the integration of traditional medicines (after their evaluation) with primary healthcare systems (Anon, 1978a). The difficulties encountered in merging traditional medicines with Western style medicine are vastly different in developing countries than in industrialised countries. In the latter, the majority of the population live in a society where Western-style medicine is the norm and concern centres around patients consulting non-qualified healers who make unsubstantiated claims. In developing countries, by far the majority of the population will depend on traditional medicine for their healthcare and, in addition to financial constraints, there is a strong cultural belief and social framework to overcome. Drug utilisation studies in developing countries have suggested, for instance, that a high percentage of epileptic patients rely on traditional forms of medicine and are not receiving any anti-epileptic drugs (Danesi & Adetunji, 1994). Reasons suggested for the persistent use of traditional therapies in developing countries, despite an awareness of western scientific medicine, have included the believed origin of the illness (supernatural or natural) and previous experience (efficacy-testing hypothesis) (Danesi & Adetunji, 1994). An illness believed to be caused by supernatural forces (e.g. epilepsy) is considered the domain of traditional medicine, whereas an illness considered naturally caused can be treated with modern medicine (Danesi & Adetunji, 1994). Additional reasons provided for the low utilisation of Western medicines in developing countries include a lack of medical doctors, pharmaceutical products and money (Zhang, 1996). The WHO recognises that traditional medicine may not be readily transferable from one culture to another, and therefore encourages countries to exploit those aspects of traditional medicine that

provide safe and effective remedies or practices for use in primary healthcare (Akerele, 1988).

1.2 Complementary Medicine in Industrialised Countries

The concept of complementary medicine exists in Western countries and represents therapies that fall outside the recognised orthodox system of medicine. Various terms have been used to describe non-orthodox therapies including unconventional, non-orthodox, fringe, natural, complementary and alternative. Throughout this thesis, the phrase complementary medicine (CM) will be used when referring to non-orthodox therapies. CM is considered to overlap the professional and folk healthcare sectors (Helman, 1994), but its use is often influenced by the popular sector. Orthodox medicine can be defined as being based on the understandings of the body which are widely accepted in Western society, legitimised by scientific study, subject to state regulation, and with standards of practice enforced to protect the patient (Sharma, 1992). However, alongside orthodox medicine exist a plethora of complementary therapies which have been steadily gaining in popularity since the 1970's. It is interesting to try and understand why there has been such a continued interest in CM when often this option represents a more expensive one for the patient. Consumer surveys show positive public attitudes to CM, with about 60% of the public in the Netherlands and Belgium willing to pay extra health insurance premiums for it, and 74% of the British public favouring availability on the National Health Service (NHS) (Fisher & Ward, 1994).

Today, we are all encouraged to lead a "healthy lifestyle" and articles discussing ways to improve our health are common place in the lay press. In addition, many media articles highlight the potential dangers of conventional drugs and surgical procedures. This combined with the familiar scenario of short general practitioner (GP) consultations and long waiting times for the treatment of non-life threatening conditions, have undoubtedly contributed to a growing interest in alternative methods of healthcare. Studies investigating the reasons why patients choose CM have reported a

disenchantment with orthodox medicine as the stimulus in some individuals, whereas other patients are drawn to CM because of a strong belief in the philosophy of the particular therapy chosen (Furnham & Forey, 1994), or simply as an addition to their orthodox treatment (Donnelly et al, 1985). Indeed it has been established that many patients use orthodox and non-orthodox treatments concomitantly (Boisset & Fitzcharles, 1994), choosing orthodox medicine for those illnesses perceived as more serious (Furnham & Forey, 1994). Other features noted of patients who use CM include a greater scepticism of the efficacy of conventional GPs in treating illnesses, a greater belief in the efficacy of CM, and a greater understanding of the biological and physiological functioning of the body (Furnham & Forey, 1994).

Studies have reported that patients turn to CM for chronic conditions which are disruptive of normal life rather than being life-threatening, such as musculo-skeletal disorders, chronic pain, allergic conditions, and stress-related and psychosomatic problems (Sharma, 1992). Various psychological studies have reportedly shown that the incidence of unproven remedy use is much higher in diseases for which the cause is unknown (Wasner, 1984). It is generally recognised, for instance, that complementary therapies are popular among patients with rheumatic diseases, and many studies have investigated the use of CM in this patient group (Boisset & Fitzcharles, 1994; Kestin et al, 1985; Vecchio, 1994; Visser et al, 1992; Wasner, 1984). A Dutch survey, of patients with rheumatic diseases reported that almost half had visited a complementary practitioner, with hand healers, homoeopaths and acupuncturists the most frequently visited (Visser et al, 1992). Recognising this, the Dutch Association of Rheumatologists officially advised its members in 1981 to respect the wishes of a patient to try an alternative treatment and to seek to retain the care of the patient (Visser et al, 1992). In Australia, a survey of patients with rheumatoid arthritis reported a high prevalence of use of unproven remedies, although only a minority of these remedies were obtained via a complementary practitioner. The majority were obtained from either chemists or health food stores (Kestin et al, 1985). Another Australian survey of rheumatology out-patients concluded that whilst many will have used at least one complementary therapy (40% in this study), these patients were no more dissatisfied with their orthodox treatment than the patients who had not used a complementary therapy (Vecchio, 1994).

Encouragingly, the patients who sought alternative treatments considered their rheumatologist to be interested and supportive of their use of complementary therapies. In Canada, a survey of rheumatology out-patients reported a 66% prevalence of current use of CM, with the majority either buying over the counter products or using spiritual aids such as prayer, relaxation or meditation, and a minority visiting complementary practitioners (Boisset & Fitzcharles, 1994). In Canada, a survey of 2055 children presenting to a paediatric out patient clinic, reported that 11% of parents had used CM for their child (Spigelblatt et al, 1994). Children who used CM tended to be older than non-users, have better educated mothers, and have parents who used CM. The major factor influencing the use of CM was word of mouth, with fear of conventional drug side-effects and a chronic medical problem also representing key influences. Of lesser importance were dissatisfaction with conventional medicine and more personalised attention. In the US, a telephone survey of 1539 adults carried out in 1990 reported that 34% had used a complementary therapy in the previous year (Eisenberg et al, 1993). Complementary therapies were reported to have been used primarily for non-life threatening conditions such as back problems, anxiety, headaches and chronic pain. Reassuringly, patients with a more serious medical condition who used a complementary therapy also sought the advice of a conventional medical practitioner.

Interest in CM has not only increased among the lay public but also among orthodox GPs. In Germany, for instance, it has been reported that the percentage of doctors practising solely mainstream medicine decreased from 30% in 1971 to 5% in the early 1990s (Himmel et al, 1993). Over a third of France's 54,500 GPs use CM, 5% exclusively, 21% often, and 73% occasionally (Fisher & Ward, 1994). In the Netherlands, a growing number of general practitioners and physiotherapists is practising complementary methods themselves, most commonly homoeopathy (40%), manipulation (9%), and acupuncture (4%) (Fisher & Ward, 1994; Visser et al, 1992). In the Netherlands, the percentage of people who visited a complementary healer increased by 0.3% per annum between 1981 and 1990, and the number of patients visiting a medical practitioner providing a complementary therapy rose by 1% per annum over the same period (Menges, 1994). In Germany, a survey of 40 GPs reported that doctors used complementary therapies for patients with chronic disease, psychosomatic

disorders, minor illnesses, and terminal illnesses (Himmel et al, 1993). Reasons given by the doctors for choosing to use complementary therapies were prior therapeutic success, failure of orthodox medicine, scarcity of adverse reactions, and patients' requests. It is logical that a physician is unlikely to feel comfortable considering a request to use complementary therapies by a patient with an acute, serious illness, whereas when the illness is more chronic there is time to consider and discuss the request. Unlike Europe, in the United States the status of registered osteopaths and chiropractors is recognised alongside that of orthodox medically qualified practitioners (Wardwell, 1994).

Table 1.1 Most Frequently Occurring Forms of Complementary Medicine in Nine European Countries[1]

Country	Form of Complementary Medicine (in descending order of popularity)									
	1	2	3	4	5	6	7	8	9	10
Belgium	HO	MH	AC	CH	OS	NA	HR	PH	HY	AM
Denmark	CH	AC	HY	MA	IR	ZT	ST			
Finland	HR	MA	CH[2]	AC	HO	CU	FH	AM		
France	HO	AC	HR	WC	CH	TH	OS	IR		
Great Britain	HR	OS	HO	AC	CH	HE	HY	RE	NA	AR
Italy	HO	AC	HR	PT	CH					
Netherlands	HO	HR	MH[3]	PH	AC	DT	NA	AM		
Switzerland	HO	MT	AC	HR	RE	DO	HY[4]	AM	MA	
West Germany	HO	AC	PIT	CH	OT	HR	HP	PS	MA	CT

Key

(AC) Acupuncture (MH) Manual Healing

(AM) Anthroposophical Medicine (MA) Massage

(AR) Aromatherapy
(CT) Cell Therapy
(CH) Chiropractic
(CU) Cupping
(DT) Diet Therapy
(DO) Dowsing
(FH) Faith Healing
(HE) Healing
(HR) Herbal Remedies
(HO) Homoeopathy
(HP) Humoral Pathology
(HY) Hypnotherapy
(IR) Iridology
(MT) Manipulation Techniques
(NA) Naturopathy
(OS) Osteopathy
(OT) Ozone + Oxygen Therapy
(PH) Paranormal Healing
(PT) Prana Therapy
(PIT) Procaine Injection Therapy
(PS) Psychotherapy
(RE) Reflexology
(ST) Sound Therapy
(TH) Thalassotherapy
(WC) Water Cures
(ZT) Zone Therapy

[1] Sharma, 1992

[2] Chiropractic + naprapathy + bone setting

[3] Chiropractic + osteopathy + manipulation

[4] Hypnotherapy + psychotherapy + sophrology

Table 1.1 lists the most frequently used forms of alternative medicine in various European countries (Sharma, 1992), and is based on data collected for the Belgian Consumers' Association in 1987. In addition to the considerable inter-country variation in popular therapies, it is important to note that homoeopathy ranks the most popular therapy in six countries, and that herbal remedies are among the top four most popular therapies in six out of the nine countries surveyed. Denmark is the only country not listing herbal remedies, and interestingly homoeopathy, as popular therapies.

Other authors have commented on the difference in therapy use between member states, although differences in the definition of CM and of individual therapy terms can make cross-country comparisons difficult. In Germany, for instance, the most popular forms

of therapies used by doctors have been reported to be herbal medicine, neural therapy, homoeopathy, and chiropractic treatment (Himmel et al, 1993). In other European countries commonly used therapies are homoeopathy, acupuncture and manipulative therapies (Himmel et al, 1993). Popular therapies are reported as acupuncture, homoeopathy and hand healing in the Netherlands, herbalism and homoeopathy in the UK, and chiropractic, relaxation and massage in the United States (US) (Boisset & Fitzcharles, 1994).

Concerns that have been raised about the use of CM include the cost to the patient, undermining of the doctor-patient relationship, possible delays in effective medical treatment, and possible harmful side-effects. However, various studies of patients who use complementary therapies have perhaps surprisingly reported a general satisfaction with orthodox medicine, a good relationship with their orthodox practitioner who is usually informed about any intended use of CM, and an intention to use conventional medicine for any future problems (Donnelly et al, 1985; Himmel et al, 1993; Moore et al, 1985; Vecchio, 1994; Visser et al, 1992). Awareness by orthodox doctors of their patients' use of complementary therapies seems to differ between countries, for example being much lower in the United States than in the Netherlands. This difference has been attributed to a greater acceptance of complementary therapies in Europe (Boisset & Fitzcharles, 1994).

1.3 Complementary Medicine in the UK

As summarised in the British Medical Association (BMA) report on complementary medicine (Anon, 1993c), the freedom for patients to exercise personal choice in who they seek medical treatment from has a long history. In 1511, an Act was passed which established the College of Physicians of London with sole right to practice within a radius of 7 miles. In 1543, an amendment to the Act recognised gratuitous advice by, for example, apothecaries. The dominant status of western-style, scientific based medicine as the orthodox healthcare system in the UK was formalised by the 1858 Medical Act, under which it

became illegal for any person who had not been registered as a qualified medical practitioner to claim to be one. Initially the 1858 Bill contained a clause banning doctors from practising "unconventional" forms of medicine, but this was rejected by both Houses of Parliament (Anon, 1993c). Over the last one hundred years or so, the professional sector has recognised and absorbed many therapies from the folk sector such as midwifery (1902), pharmacy (1852 and 1868), dentistry (1878), and homoeopathy (1948) (Helman, 1994).

The discovery of drugs such as penicillin, streptomycin and chloramphenicol in the third and fourth decades of the twentieth century marked a decline in the popularity of non-orthodox therapies, which could not compete with the dramatic results obtained with the new wonder drugs. The National Insurance Act of 1911 and the National Health Services Act of 1948 strengthened the relationship between orthodox medicine and the state by vastly increasing the scope of public medical services (Inglis, 1992), but included homoeopathy.

Although there has been a renewed interest in CM over the last 20-30 years, many therapies have a long traditional history. Herbalism, faith healing and midwifery probably have the deepest roots in the UK.

Other forms of healing, such as acupuncture, homoeopathy, osteopathy and shiatsu have been imported from abroad (Helman, 1994). Homoeopathy has a special status in the UK, having been associated with the Royal Family since King George VI's reign.* The first homoeopathic hospital was founded in London in 1849, and homoeopathy reached a peak of popularity in the second half of the nineteenth century (Nicholls, 1992). In 1948 homoeopathy was incorporated into the National Health Service (NHS) and there are currently NHS homoeopathic hospitals in London, Liverpool, Bristol, Tunbridge Wells and Glasgow (Helman, 1994). The hospitals are staffed by doctors trained in orthodox medicine with postgraduate qualifications in homoeopathy. The evidence supporting the use of acupuncture in pain relief led to the establishment of two acupuncture clinics in NHS hospitals, in Poole and Brighton (Fulder, 1984).

*Since Prince Albert's (Victoria) time, certain forms of acupuncture have been used by pain clinics.

In the UK, anyone can practise as a non-conventional practitioner irrespective of their training. However, an unqualified practitioner cannot claim to be, or practise as, a registered medical practitioner, pharmacist, midwife, dentist, or osteopath, or imply to be a state registered chiropodist, dietician, medical-laboratory technician, occupational therapist, physiotherapist, radiographer or orthoptist. Practitioners of non-conventional medicine cannot advertise to treat various conditions, including cancer, tuberculosis, diabetes, glaucoma and epilepsy, although they can treat patients with these conditions. Moreover, a non-conventional practitioner is not permitted to treat a patient with a sexually transmitted disease (Anon, 1993c).

Table 1.2 Numbers of Complementary Therapists in the UK (1981/1982)[1]

Therapy	Medically Qualified	In Professional Association	Not in Profess. Association	Total
Acupuncture	160	548	250	958
Alexander (teachers)	5	170	50	225
Chiropractic	1	156	200	357
Hakims, Chinese Doctors	0	40	40	80
Healing	20	6,300	13,000	19,320
Herbalism	10	228	200	438
Homoeopathy	425	41	230	696
Hypnotherapy	1,000	507	170	1,677
Massage/ Manipulation	350	1,000	1,500	2,850
Misc. Physical Therapies	0	300	800	1,100
Music/Art/ Drama Therapy	0	815	90	905
Naturopathy	5	204	200	409
Osteopathy	212	777	150	1,139
Radionics	21	98	100	219
Totals	**2,209**	**11,184**	**16,980**	**30,373**

[1]Fulder, 1984

Today, a vast array of complementary therapies is available in the UK. In 1981/1982 Fulder estimated the numbers of complementary therapists in the UK (Table 1.2) (Fulder, 1984). Despite being some 15 years out of date, this survey was particularly comprehensive and to-date has not been updated by a survey of similar scope. The numbers shown in columns one and two represent those practising therapists who belonged to a professional organisation. Many therapists do not belong to professional organisations, and an estimate was therefore made to account for these individuals (column three). Fulder noted that even when healing and music/art/drama therapy were excluded, the number of complementary therapists in a professional association or medically qualified represented 15% or 8% of GPs, respectively. These numbers, particularly of those therapists not in a professional association, denote a minimum and today the number of therapists will have undoubtedly increased considerably. In 1980/1981, a survey of CM practitioners estimated there to be approximately 12 practitioners per 100,000 population, and 2 million annual consultations each for acupuncture, osteopathy, and chiropractic (Fulder & Munro, 1985). Thomas et al (1991) estimated that in 1987 there were 1909 non-medically qualified practitioners actively practising as a member of one of the main professional associations in the UK for acupuncture, chiropractic, homoeopathy, herbalism, naturopathy with osteopathy, and osteopathy. Practitioners' self-estimates of workload indicated a total of four million consultations during 1987, approximately 1 per 55 patient consultations with an NHS GP (Thomas et al, 1991).

In the 1980's, three UK surveys assessed the usage of different kinds of CM (Table 1.3). Whilst the surveys indicated osteopathy, homoeopathy, acupuncture, chiropractic, and herbal medicine as consistently popular forms of CM, there were also notable inter-survey differences in the stated usage of individual therapies. For instance, osteopathy ranged from 6% to 42%, homoeopathy from 4% to 26%, acupuncture from 3% to 23%, and chiropractic from 2% to 22%. Whilst herbal medicine usage was consistent in two of the polls, it was absent from the MORI 1989 poll. These figures highlight the difficulties inherent in interpreting the stated results of alternative therapy popularity surveys. Of the three surveys the Which? poll was based on a random subset of readers who claimed to use CM and may not, therefore, be based on a representative sample.

Table 1.3 Usage of different kinds of Complementary Medicine in the UK showing Relative Popularity[1]

RSGB[2] 1984		Which? 1986[3]		MORI 1989	
Herbal medicine	12%	Osteopathy	42%	Homoeopathy	11%
Osteopathy	6%	Homoeopathy	26%	Osteopathy	10%
Homoeopathy	4%	Acupuncture	23%	Faith Healing	5%
Acupuncture	3%	Chiropractic	22%	Acupuncture	4%
Chiropractic	2%	Herbalism	11%	Chiropractic	4%
Spiritual healing	2%			Hypnosis	3%
Hypnotherapy	2%				
100%=representative sample of 2023		100%=random sample of 1942 from unspecified number of readers who claimed to have used CM		100%=representative quota sample of 1826 adults	

[1] From Sharma, 1992 [2] Research Surveys of Great Britain

[3] Anon, 1986d

Responses provided to additional questions in the 1986 Which? survey (Anon, 1986d) are shown in Table 1.4. The responses indicate a high level of dissatisfaction with orthodox medicine especially for joint problems (most common reason for seeking CM), and a high level of satisfaction (31% cured, 51% improved) with the complementary therapy used. These results indicate the value of CM in treating non-acute, non-life threatening conditions such as joint problems. The complementary, rather than alternative nature of non-orthodox therapies has been highlighted by studies

Table 1.4 Results of Which? Survey 1986[1]

Most common problem complementary medicine used for	Pain or joint problem Psychological problem	71% 15%
Conventional medicine tried for the problem	Yes	81%
Opinion of conventional medicine received	Dissatisfied due to lack of cure, temporary relief only, or no treatment available	81%
Opinion of complementary medicine received	Cured Improved Would use form of CM again Would recommend form of CM to someone with similar complaint Ineffective Problem became worse	31% 51% 74% 69% 14% 1%
Asked GP for help in finding a complementary practitioner	No: Thought GP would disapprove of CM or of seeking a second opinion from any practitioner	90%

[1] Anon, 1986d

of CM users (Murray & Shepherd, 1988; Thomas et al, 1991). Of the patients surveyed by Thomas et al, the majority (64%) had sought orthodox treatment before using a complementary therapy and 24% of this group were receiving orthodox treatment concurrently. The 36% of patients who had not sought orthodox treatment prior to a complementary therapy were reported to have less contact with their GP compared to the other group. By far the majority (78%) of complementary therapy treatments were sought for musculoskeletal problems, and patients suffering from atopic conditions,

headaches, and arthritis were most likely to report a concurrent use of orthodox and CM (Thomas et al, 1991).

The increasing public interest in CM has been paralleled by a growing interest amongst orthodox doctors. Three quarters of fundholding GPs are reportedly in favour of CM availability on the NHS, in particular osteopathy but also acupuncture, chiropractic, and homoeopathy (Fisher & Ward, 1994). Various surveys of GPs, GP trainees and hospital doctors have reported a willingness to refer to complementary practitioners, an interest to be trained in some form of CM (15-42%) with 12-38% having already received some aspect of training, and between 10-20% currently treating with a complementary therapy (Anderson & Anderson, 1987; Perkin et al, 1994; Taylor-Reilly, 1983; Wharton & Lewith, 1986). Interestingly, despite a reported high referral rate to complementary practitioners and a desire for complementary practitioners to be covered by statutory legislation, the knowledge of practitioner qualifications amongst referring doctors was low (Perkin et al, 1994). Up to 37% of GPs are reported to use homoeopathy (Fisher & Ward, 1994).

In view of the increasing interest in complementary therapies, the BMA commissioned a report into alternative therapies which was published in 1986. The report stated that it aimed to "consider the feasibility and possible methods of assessing the value of alternative therapies, whether used alone or to complement other treatments...." (Anon, 1986e). Notably, the working party did not contain anyone with a specific expertise in alternative therapies. Therapies covered by the report were acupuncture, aromatherapy, Bach flower remedies, healing, hellerwork, herbalism, homoeopathy, hypnotherapy, iridology, macrobiotics, naturopathy, orthomolecular treatment, osteopathy and chiropractic, polarity therapy, radionics, and reflexology, although only a few of these were discussed in any detail. The report rather negatively concluded that "whilst an assessment of alternative therapies is feasible it may not be either necessary or desirable". This conclusion was disappointingly received by the medical profession, who considered it "pays a tribute to the achievements of modern medicine and presents a largely negative appraisal of alternative methods of treatment" (Anon, 1986b). It was considered that the working party approached the review with "a closed mind, already

precluding the necessity or desirability of alternative therapies" (Anderson & Anderson, 1986). Indeed, a number of surveys carried out before or around the time of the BMA report had indicated considerable interest amongst UK GPs in complementary therapies (Anderson & Anderson, 1987; Taylor-Reilly, 1983; Wharton & Lewith, 1986). The British Holistic Medical Association was also critical of the report, particularly in respect of the lack of any primary healthcare or alternative therapy experience by the members of the working party (Anon, 1986c).

In 1993, the BMA published a second more positive report entitled Complementary Medicine, New Approaches to Good Practice (Anon, 1993c). The report followed discussions of a working party set up in 1990 by the BMA Board of Science and Education with the following terms of reference: "to consider the practice and use of complementary medicine since 1985 throughout the UK and the European communities and its implications after 1992". The chapter on non-conventional therapies in Europe discussed the difficulties in achieving harmonisation of the regulation of such therapies. The report concluded that in view of the diversity in practice and control of non-conventional therapies across Europe, it was difficult to envisage future European legislation harmonising the regulation of such therapies. However, European legislation was expected to have a considerable impact on the availability of specific therapies such as homoeopathy and herbal medicine. This has indeed been the case, and the legislation of herbal medicines in the UK is discussed in Chapter 2 of this thesis. With respect to the UK, the report concluded there is a wide range of complementary therapies practised in the UK, a growing number of therapists, an increasing number of people using such therapists, and an increasing interest among orthodox practitioners. The report was open to complementary practitioners working alongside orthodox doctors, but stressed the need for formal registration and recognised levels of competence for complementary therapists, an increased understanding of and, where desired, training in complementary techniques by orthodox doctors, and a closer collaboration between the medical profession and complementary therapists in clinical research. With respect to research, the report concluded that priority should be given to those therapies most commonly used in the UK, namely osteopathy, chiropractic, homoeopathy, acupuncture and herbalism. These most popular complementary

therapies were obtained from a survey conducted by the Consumers Association in 1991 on behalf of the BMA Board of Science and Education. Other therapies reported in the survey to be widely used included aromatherapy, reflexology and hypnotherapy (Anon, 1993c).

CM is considered to span both the professional and folk sectors (Helman, 1994). The dominant role of the professional sector in the UK and the belief by many complementary practitioners that CM should truly be complementary to orthodox medicine, has resulted in the professionalisation of many therapies. Formal qualification requirements and registration of members will hopefully not only assist in the integration of CM with orthodox medicine, but also protect the public from unqualified practitioners who create a negative and unprofessional image of CM. The recent recognition of osteopathy by the professional healthcare sector in 1993 is a positive step in this integration process (Anon, 1993b). It is also encouraging that a study by the National Association of Health Authorities and Trusts of the present use of CM within the NHS is currently underway (Ernst & Barnes, 1996). The study aims to collect data from NHS purchasers and providers on several key aspects, such as policies on CM, referral procedures, supervision, qualifications and experience of complementary practitioners, and the recording of outcome, benefits and costs.

1.4 Pharmacy Involvement with Complementary Therapies

For several years there has been an increasing trend for individuals to purchase their own medicines rather than obtain them via their GP. The range of over-the-counter medicines has multiplied and campaigns encouraging patients to "Ask their pharmacist" have further stimulated this aspect of the popular healthcare sector. Two identical surveys of 500 patients attending a GP's surgery in 1970 and 1985 reported the percentage of patients consulting a pharmacist about their health problems to have increased from 10.8% to 16.4% over the fifteen year interval (Elliott-Binns, 1986). More recently, the trend to deregulate medicines from Prescription Only to Pharmacy

Only (Edwards & Stillman, 1995) has further encouraged the self-treatment of medical conditions. Purchase of many of the new Pharmacy Only medicines, such as H_2-antagonists and imidazole antifungals, highlights an interesting overlap between the popular and professional healthcare sectors.

The increasing trend to use self-prescribed complementary therapies has not gone unnoticed by retail pharmacists. The number of pharmacies stocking complementary remedies such as herbal and homoeopathic products, Bach flower remedies, and aromatherapy oils has increased dramatically over the last decade. This is not unexpected when the quoted statistics for the market value of complementary remedies are considered. Sales of natural medicines including vitamins, minerals, dietary supplements, and herbal products were estimated at £200 million in 1990 (Anon, 1993c). The essential oil market is reportedly worth about £10 million (Anon, 1996d).

Of the many complementary therapies available in the UK, the key areas in which pharmacists are becoming increasingly involved are in the sale and supply of homoeopathic products, healthfoods and nutritional supplements, and herbal products.

1.4.1 Homoeopathic Products

The founder of modern homoeopathy was a German physician Samuel Hahnemann, who practised in the late eighteenth and early nineteenth centuries. The basic principle of Hahnemann's theory ("Let likes be treated by likes") was that a substance which produces specific symptoms in large doses can be used to treat the same symptoms when taken in much smaller doses. Hahnemann believed that successive dilutions of a mother tincture reduced the potential harmful effects of a treatment and enhanced the therapeutic activity. Successive dilutions are named potencies and each dilution is followed by a succussion (specific method of mixing/shaking). Dilutions can be made in multiples of 1 in 10 (nx), 1 in 100 (nc), or 1 in 1000 (nm), where "n" denotes the number of dilutions (Cook, 1989). Homoeopathy was first introduced into the UK by

Dr Frederick Hervey Foster Quin in 1832, and there followed a rapid growth in the popularity of homoeopathy between 1850 and 1900 (Cook, 1989).

Despite the claims of orthodox medicine that most homoeopathic medicines are too dilute to contain a single molecule of the original mother tincture, the Faculty of Homeopathy was recognised in 1952 and FP10 prescriptions are re-imbursable (Ainsworth, 1996). It is estimated that since the 1970's the number of people receiving homoeopathic treatment in the UK has trebled. A survey conducted by the Institute for Complementary Medicine in 1984 reportedly showed that the number of homoeopathic patients exceeds one million and is increasing by 15-20% per annum (Cook, 1989). The UK homoeopathic market has reportedly increased in value from £12 million to £16 million over the last three to four years (Kayne, 1996), further reflecting the increased use of these medicines.

Although today there are over three thousand homoeopathic medicines available, the two hundred or so remedies proved by Hahnemann and his co-workers are the most commonly used. Homoeopathic medicines may be classified according to their origin or source (plant/vegetable, animal, chemical/mineral, biological), or their manner of application (specific, polychrest, constitutional, combination or single remedies). Specific, single, combination and polychrest (common remedies for a wide range of symptoms) remedies are all symptom related, whereas constitutional remedies are more orientated to a patient's characteristics (Cook, 1989). In addition to the presenting symptoms, a homoeopathic practitioner will consider many aspects of a patient's lifestyle and constitution when considering the most suitable homoeopathic prescription. However, because certain core remedies have been associated with treating a particular set of symptoms, at a simplified level the principle of using homoeopathic medicines also lends itself to self-treatment (for chronic, non-serious conditions). Many homoeopathic medicines are now manufactured for over-the-counter purchase, with guidance notes designed to assist the customer in choosing the most appropriate product for their symptoms.

Under the Medicines Act 1971, all homoeopathic medicines in a greater dilution of 1 part per million (6x) are exempt from restrictions and can be supplied by lay practitioners and sold in shops (Fulder, 1984). On January 1 1994 two European Council directives on homoeopathic medicinal products and homoeopathic veterinary medicinal products came into force, intending to ensure a single European market for these products. The directives cover the manufacture and inspection, marketing, and labelling of homoeopathic medicinal products. Provision has been made for a simplified system of registration for medicines containing less than one part per 10,000 of the undiluted mother tincture (Fisher & Ward, 1994).

The number of pharmacies stocking homoeopathic medicines has increased dramatically from only five in 1977, to five thousand in 1989 (Cook, 1989). The education of pharmacists to enable their provision of professional advice on the sale of homoeopathic medicines is essential. A Council statement in June 1986 from the Royal Pharmaceutical Society of Great Britain rather negatively advised pharmacists that homoeopathic medicines were unsuitable for over-the-counter recommendation due to the lack of scientific evidence regarding their efficacy (Anon, 1986f). This advice is not really practical in view of the considerable popularity of homoeopathic medicines. Postgraduate training courses are now available for pharmacists in London and Glasgow (Kayne, 1996), and the Homoeopathic Pharmacists Association aims to provide pharmacists with a conceptual framework from which to make professional judgements (Anon, 1988a). In the longterm, the Association aims to introduce some element of homoeopathic teaching into the undergraduate pharmacy course.

1.4.2 Healthfoods / Nutritional Supplements

Multivitamin and mineral supplements represent a growing consumer market and today the majority of pharmacies stock at least a limited range of these products. A Seven Seas report claimed the multivitamin and mineral supplement market grew by 7% in 1995 to a value of £280 million. The market share was divided between cod liver oil

and fish oils (30%), multivitamins (20%), other supplements (16%), evening primrose oil / starflower oil (12%), single vitamins (14%) and garlic (8%) (Anon 1996d). Pharmacists need to be able to provide factual and objective advice on not only the traditional vitamin and mineral supplements, but also on more recently introduced products such as slimming aids, ginkgo, guarana, selenium, co-enzyme Q-10, and melatonin. Many of these newer products are advertised widely in the laypress, and in health and womens magazines, prompting a sudden consumer demand. It is important that pharmacists remain up-to-date with new products introduced to the market and remain abreast of any safety issues, as with laetrile and apricot pits, vitamin A, tryptophan, germanium, and melatonin (Anon, 1996e; DeSmet, 1992).

1.4.3 Herbal Products

Herbal medicine has a long history of traditional use in the UK.

The largest herbal printed in English was compiled in 1636 by John Parkinson and contained descriptions of the medicinal use of some 3800 plants. Herbals published in subsequent centuries consisted mainly of rewriting of earlier works (Hyde, 1978). The social transformation of the UK to an industrialised society towards the end of the seventeenth century and the beginning of the eighteenth century resulted in a working class without the financial access to orthodox practitioners. Opportunities arose for the fraudulent sale of pre-packaged medicinal preparations, often containing irrational combinations of ingredients, to ignorant customers. Herbal products remained the main source of medication for the working class until the NHS was established in 1948, after which their popularity declined (Shellard, 1987).

During the eighteenth century, the discovery of active principles such as alkaloids and essential oils laid the foundations of phytochemistry and the pharmacological assessment of herbal medicine (Hyde, 1978). During the first half of the twentieth century, the number of herbal remedies included in Western pharmacopoeias gradually declined, reflecting their demise in popularity. However, the second half of this century

has seen a steady increase in both the screening of plants for medicinal compounds and in the public interest in herbal medicines.

The recent resurgence of interest in herbal medicines has seen another opportunity for herbal product manufacturers to produce attractively packaged remedies, often containing irrational combinations of herbs. In addition, a plethora of books bestowing the virtues of various remedies have flooded the laypress. Under legislation laid down by the Medicines Act (1968), the government has sought to rationalise the ingredients present in herbal medicines. This action culminated in the Review of Herbal Medicines and is discussed further in Chapter 2. Effective legislation of herbal remedies as medicines has been a topical issue for many years, and the current harmonisation of European medicines legislation has served to highlight many of the issues. The legislation of herbal medicines is discussed in Chapter 2.

Herbal medicines have shown a 50% increase in value since 1988 and are predicted to grow a further 8% in the EC over the next five years (Platt, 1996). Many pharmacies now stock herbal products which reportedly account for 50% of over-the-counter purchased complementary medicines (Platt, 1996). A Mintel survey reportedly indicated a trend towards pharmacy sales for herbal medicines: in 1994 pharmacies claimed 48% of the £35 million market compared with 45% in 1992, whilst health food shops declined from 50% to 42% (Anon, 1996d).

Clearly pharmacists are becoming increasingly involved in the sale and supply of herbal products. It is widely recognised that pharmacists are ideally placed to offer professional advice on the use of herbal medicines, as with any other medicine. Indeed if pharmacists are involved in the supply of herbal medicines, surely they have a professional duty to be able to provide factual advice on these products, irrespective of personal beliefs (Finberg, 1996; Madge, 1996). However, most pharmacists do not have the necessary knowledge of herbal medicines to feel comfortable offering such advice. Very few pharmacy undergraduate courses provide training on herbal remedies, and the usual reference sources used by pharmacists to obtain information on a particular medicine contain either no or little reference to herbal medicines. The increasing

involvement of pharmacists with herbal remedies was addressed at the 1981 British Pharmaceutical Conference (BPC), during which a presentation entitled "The Pros and Cons of Herbal Remedies" was given (Phillipson, 1981). The presentation covered legal aspects, products available in the UK, and issues surrounding their quality, safety and efficacy. There followed a series of articles in the Pharmaceutical Journal aimed at heightening pharmacists' awareness towards herbal remedies (Anderson & Phillipson, 1982; Baldwin et al, 1986; Baldwin et al, 1987a; Barber, 1988; Chandler et al, 1984b; Phillipson & Anderson, 1984a-f). It was clear from a discussion session on herbal medicines at the 1990 BPC, that many pharmacists were confused about the licensing requirements relating to herbal products, and that there were concerns over the availability of unlicensed herbal products as food supplements. Areas of particular concern raised by the discussion group were the lack of reliable information on the nature of the active constituents in many herbal remedies, and the problems associated with the lack of standardisation (Phillipson, 1990). In 1990, the Royal Pharmaceutical Society of Great Britain wrote to the Minister for Health requesting that the legal status of natural remedies and food supplements be reviewed and for stronger controls to be introduced (Anon, 1990b). Recent correspondence in the Pharmaceutical Journal has once again highlighted the confusion that exists over the quality control and legal status of herbal products (McCoig, 1996). Since 1990, articles have regularly appeared in the Pharmaceutical Journal on various herbs including aloe vera, evening primrose, valerian, ginkgo, echinacea, agnus castus, feverfew, chamomile, guarana, and ginseng (Berry, 1994 & 1995; Houghton, 1994a-d & 1995; Li Wan Po, 1991; Marshall, 1990; Raman & Houghton, 1995).

The increasing involvement of pharmacists in the supply of herbal medicines is paralleled by a requirement to provide professional advice on the use of these products. As with all medicines, pharmacists should be responsible for supplying herbal medicines of reliable quality, safety and efficacy, and be able to advise patients on such aspects as potential adverse reactions and drug interactions. If pharmacists are to be able to provide professional advice to customers on herbal medicines, then access to reliable information sources is required.

1.5 Aims and Objectives

The aim of the present research was to increase the pharmacist's awareness of the pharmacological properties of herbal ingredients in European herbal products.

The objectives of the research were to:

- Identify European herbal remedies available in the UK, primarily those being sold through pharmacies
- Consider the role of the pharmacist in the sale or supply of European herbal remedies
- Determine the information needs of the pharmacist to effectively perform this role
- Collate relevant data pertaining to the quality, safety and efficacy of European herbal remedies
- Establish a core reference source to meet the needs of the pharmacist with respect to European herbal remedies

2. LEGISLATION ON HERBAL REMEDIES

2.1 Product Availability in the UK

Herbal products are available from a variety of sources including pharmacies, health food stores, supermarkets, department stores, mail order catalogues, and classified advertisements in magazines with a focus on healthy living. In addition, an individual can collect their own plant material or receive a product prescribed by a herbal practitioner. The latter two sources are not discussed within the context of this thesis.

Some herbal products consist solely of loose, dried plant material; others are presented as pre-packaged formulated products in a variety of pharmaceutical forms for both internal (tablets, capsules, liquids) and external use (creams, ointments) and may contain 4-5 herbal ingredients in the form of dried plant material or their extracts. Although these pharmaceutical formulations resemble those of medicinal products, many herbal products are unlicensed (see section 2.2.3 below).

2.2 Historical UK Legislation on Herbal Remedies

Table 2.1 lists the various UK legislation that refer to herbal remedies.

2.2.1 Medicines Act 1968

The Medicines Act 1968 (MA) (Anon, 1968) was drawn up in the wake of the thalidomide tragedy and came into force in September 1971. Under the MA, a medicinal product is defined as any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for

Table 2.1 UK Legislation Affecting Herbal Remedies

Legislation	Action
Medicines Act 1968[a] Section 12	Exempts herbal remedies from restrictions imposed by Sections 7 and 8 of the Act for (a) products prepared and supplied by herbalists, and (b) products consisting solely of dried, crushed, comminuted plants sold under their botanical name and with no written recommendation of their use.
Medicines Act 1968 Section 56	Exempts herbal remedies from restrictions imposed by Sections 52 and 53 (conditions of sale for non-GSL and GSL products, respectively) of the Act.
The Medicines (Exemption from Licences) (Special and Transitional Cases) Order SI 1450 1971[b]	Enables a manufacturer to supply a herbal product without a product licence to a herbalist for his personal use.
Prescription Only Medicines (POM) Order, SI 1212 1983[c]	Confers POM status on specific hazardous plants (see Table 2.2)
The Medicines (Cyanogenetic Substances) Order SI 187 1984[d]	Confers POM status on herbal remedies (a) labelled as amygdalin, laetrile, or vitamin B_{17}, or (b) with a cyanogenetic glycoside content exceeding 0.1%w/w
The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977 SI 2130[e]	Identifies non-POM plants unsuitable for inclusion under exemption conferred by section 56. Part I: lists 25 plants restricted to sale through a

Legislation	Action
	pharmacy (see Table 2.4) Part II: lists 19 additional plants which may be supplied by a herbalist in accordance with doses specified in Part III
The Medicines (Labelling and Advertising to the Public) Regulations 1978[f]	Specifies wording required on the labelling of licensed herbal remedies
The Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994 SI 3144[g]	Implemented EC Directive 65/65 into UK medicines legislation

[a]Anon 1968 [b]Anon 1971 [c]Anon 1983b [d]Anon 1984c [e]Anon 1977 [f]Anon 1978b [g]Anon 1994a

use wholly or mainly (in humans or animals) for a medicinal purpose. The MA specifically states that this includes the retail sale of herbal remedies.

A medicinal purpose is defined as one of:

(a) treating or preventing disease
(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition
(c) contraception
(d) inducing anaesthesia
(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by terminating, reducing or postponing, or increasing or accelerating, the operation of that function in any other way

Sections 7 and 8 of the MA provide general provisions for dealing with medicinal products, including manufacture and wholesale dealing. Sections 52 and 53 of the MA provide the conditions for the sale or supply of medicinal products not on the General Sales List and those on the GSL, respectively.

The MA recognises the potentially hazardous nature of certain plants such as digitalis, nux vomica and rauwolfia (see Table 2.2). These plants are specifically controlled under the MA as Prescription Only Medicines (POM) (SI 1212) (Anon, 1983b).

Table 2.2 Plants Included in The Medicines (Products Other Than Veterinary Drugs) (Prescription Only) Order 1983 SI 1212[1]

Herbal Material	Circumstances Excluding Medicinal Products from the Class of POMs			Comment/Key Constituents
	Maximum Strength	Use, form, route	MD, MDD[2]	
Aconite	1.3%	External		Dried roots of *Aconitum napellus*; alkaloid aconitine
Belladonna Herb Belladonna Herb		Internal External	1mg of the alkaloids (MDD)	*Atropa belladonna*; atropine
Belladonna Root Belladonna Root		Internal External	1mg of the alkaloids (MDD)	*Atropa belladonna*; atropine
Cocculus Indicus				Dried fruits of *Anamirta*

Herbal Material	Circumstances Excluding Medicinal Products from the Class of POMs			Comment/Key Constituents
	Maximum Strength	Use, form, route	MD, MDD[2]	
				cocculus; picrotoxin
Conium Leaf	7%	External		Hemlock; coniine
Digitalis Leaf, Digitalis Prepared				Digoxin; cardioactivity
Ergot Prepared				*Claviceps purpurea*; ergotamine
Gelsemium			25mg (MD) 75mg (MDD)	*G.nitidum*; indole alkaloids
Ignatius Bean				*Strychnos ignatii* seeds; strychnine
Jaborandi				*Pilocarpus* species; pilocarpine
Mandragora autumnalis				Mandrake; atropine
Nux Vomica Seed				*Strychnos nux-vomica*; strychnine
Podophyllum, Podophyllum				Lignans in the resin; cytotoxic

Herbal Material	Circumstances Excluding Medicinal Products from the Class of POMs			Comment/Key Constituents
	Maximum Strength	Use, form, route	MD, MDD[2]	
Indian, Podophyllum Resin	20%	External		
Poppy Capsule				*Papaver somniferum*; opium alkaloids
Rauwolfia Serpentina, Rauwolfia Vomitoria				Reserpine
Sabadilla				Veratrine, an alkaloid mixture resembling aconite
Veratrum (Green and White)				*Veratrum viride & V.album*; steroidal alkaloids

[1]Anon, 1983b [2] MD=Maximun Dose MDD=Maximum Daily Dose

The Medicines (Cyanogenetic Substances) Order (SI 187) (Anon, 1984c) was passed in 1984, conferring POM status on herbal remedies containing more than 0.1%w/w of this class of constituent or on those products stated to contain amygdalin, laetrile or vitamin B_{17}. The legislation resulted from considerable concern over the use of cyanogenetic glycoside-containing natural remedies (notably apricot kernels and laetrile, a semi-synthetic derivative of a cyanogenetic glycoside called amygdalin) to treat cancer (see section 4.2.6).

2.2.2 Exemptions for Herbal Remedies

Sections 12 and 56 of the Medicines Act (MA) provide exemptions for herbal remedies (summarised in Applebe & Wingfield, 1993). A herbal remedy is defined as:

"a medicinal product consisting of a substance produced by subjecting a plant or plants to drying, crushing or any other process, or a mixture whose sole ingredients are one or more substances so produced and water or some other inert substance"

Section 12 of the MA exempts herbal remedies from the restrictions imposed by Sections 7 and 8, for products prepared and supplied by medical herbalists on their own recommendation, and for products comprising solely of dried, crushed or comminuted plants sold under their botanical name with no written recommendation as to their use. These exemptions were intended to give herbal practitioners flexibility in preparing their own remedies for individual patients without the burden of licensing, and to enable simple dried herbs to be readily available to the public. In addition Article 2 of the Medicines (Exemption from Licences) (Special and Transitional Cases) Order 1971 (Anon, 1971), enables a manufacturer to supply a herbal product to a medical herbalist for his personal use within his business, without the product requiring a licence.

Section 56 of the MA further exempts herbal remedies from restrictions imposed by Sections 52 and 53, namely non-GSL products to be sold only via pharmacies and the conditions of sale for GSL products through non-pharmacy retail outlets. Herbal drugs currently included in Table A (internal or external use) to Schedule 1 of the GSL (1984 as amended by 1985, 1987, 1989, 1990 and 1994) (Anon, 1984b) are listed in Table 2.3.

Table 2.3 Herbal Drugs Included in Table A (Internal or External Use) to Schedule 1 of the GSL 1984[a](as amended 1985, 1987, 1989, 1990, 1994)

Acerola[5]	Agnus castus (Chaste Tree)[5]	Agrimony (Triticum)[3]
Aloes, Barbados/Cape[4] (50mgMD)/(100mgMD)	Angelica	Aniseed (Anise)[5]
Artichoke	Asafetida[3]	Avena (Oats)[3]
Balm of Gilead[5]	Barberry Bark	Bayberry[5]
Berberis[3] (MD equivalent to 500mcg berberine)	Blackberry[5]	Black Catechu[5]
Black Currant[5]	Black Haw[5]	Black Root
Bladderwrack (Fucus)[5]	Blue Cohosh (Caulophyllum)[5] (265mg MD)	Blue Flag[4] (600mg MDD)
Boldo[4] (1.5g MD)	Boneset (Eupatorium perfoliatum)[5]	Buchu[4]
Buckthorn[5]	Calamus (Sweet Flag)[5]	Calumba[5]
Capsicum	Caraway	Cardamon
Carrot	Cascara	Celery Oil[1] / Seed[2]
Centaury[5]	Chamomile	Chickweed[5]
Chondrus	Cimicifuga (Black Cohosh)[4] (200mg MD)	Cinnamon[4]
Clivers[4]	Clove[5]	Coltsfoot
Coriander[5]	Cranesbill Geranium[5]	Damiana[4]
Dandelion[5]	Echinacea	Elder
Elecampane	Fennel	Fenugreek[5]
Fig[5]	Frangula	Fumitory[5] (160mg MD)
Garlic[3]	Gentian	Ginger

Ginseng[5]	Golden Seal	Gravel Root (*Eupatorium purpureum*)[5]
Grindelia	Ground Ivy[3]	Guaiacum Resin[4] (200mg MD)
Hamamelis[5]	Heartsease[5]	Hemlock Spruce (Canadian Pine)[5] (400mg MD)
Holy Thistle (*Cnicus benedictus*)[4] (1.5g MD)	Hops (Lupulus)[3]	Horehound, White[3]
Horseradish[5]	Hydrangea[5]	Hyssop
Iceland Moss[5]	Ipecacuanha	Ispaghula
Jamaica Dogwood	Juniper	Kava[5] (625mg MD)
Kelp[5]	Kola	Lady's Mantle[5]
Laminaria	Lappa (Burdock)[4]	Lettuce (*Lactuca sativa*)[4]
Linseed	Liquorice	Lobelia (65mg MD)
Lucerne (Alfalfa)[5]	Lungwort[5]	Marshmallow Root[5]
Mate	Matricaria (German Chamomile)[4]	Meadow Sweet
Menyanthes (Bogbean, Buckbean)[3]	Motherwort[5]	Myrrh
Nettle (*Urtica dioica*)[4]	Nutmeg[5]	Oak Bark[5]
Parsley[5]	Parsley Piert[4]	Passiflora
Pellitory[5]	Peppermint	Pilewort[5]
Pleurisy Root[5]	Poke Root (Phytolacca)[5] (120mg MD)	Poplar (Aspen)[5]
Prickly Ash Bark (*Zanthoxylum clavaherculis*)[3]	Primula Rhizome Extract	Psyllium[5]
Pulsatilla	Quassia[4]	Queen's Delight[5] (320mg MD)
Raspberry[5]	Rhubarb rhizome	Rosemary[5]
Sage[4]	Sambucus	Sarsaparilla[4]

Saw Palmetto[5]	Scullcap	Senega
Senna Fruit/Leaf	Shepherd's Purse[5]	Skunk Cabbage (Symplocarpus)[5]
Slippery Elm - Powdered Bark	Squaw Vine[5]	Squill, Indian[5]
Squill, White	St Mary's Thistle	Sterculia
Stone Root[5]	Tilia (Lime Flowers)[5]	Unicorn Root, False[5]
Uva Ursi (Bearberry)[5]	Valerian	Verbena
Wahoo (*Euonymus atropurpureus*)[5]	Watercress[5]	Wheat[5]
Wild Cherry	Wild Indigo[5]	Wild Lettuce
Willow White	Wood Betony[5]	Yarrow
Yellow Dock[5]		

[a] Anon, 1984b

[1]SI 1540 (1985) [2]SI 910 (1987) [3]SI 969 (1989) [4]SI 1129 (1990)
[5]SI 2410 (1994)

However, it was subsequently recognised that certain plants which although not listed as POM under the MA, are nevertheless unsuitable for inclusion under the general exemption conferred by Section 56. The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977 (SI 2130) (Anon, 1977), lists in Part I twenty five plants which can only be supplied via a pharmacy (see Table 2.4). Part II lists nineteen additional plants which can be supplied via a medical herbalist in accordance with the maximum dose and maximum daily dose specified in Part III (see Table 2.5).

Table 2.4 Plants Restricted to Pharmacy Sale by SI 1977: 2130 Part I[1]

Common Name	Botanical Source
Areca	*Areca catechu*
Canadian Hemp	*Apocynum cannabinum*
Catha	*Catha edulis*
Chenopodium	*Chenopodium ambrosioides* var *anthelminticum*
Crotalaria fulva	*Crotalaria berberoana*
Crotalaria spect.	*Crotalaria spectabilis*
Cucurbita	*Cucurbita maxima*
Duboisia	*Duboisia myoporoides* *D.leichardtii*
Elaterium	*Ecballium elaterium*
Embelia	*Embelia ribes, E.robusta*
Erysimum	*Erysimum canescens*
Holarrhena	*Holarrhena antidysenterica*
Kamala	*Mallotus philippinensis*
Kousso	*Brayera anthelmintica*
Male Fern	*Dryopteris filix-mas*
Mistletoe berry	*Viscum album*
Poison Ivy	*Rhus radicans*
Pomegranate Bark	*Punica granatum*
Santonica	*Artemisia cina*
Savin	*Juniperus sabina*
Scopolia	*Scopolia carniolica* *S.japonica*
Stavesacre Seeds	*Delphinium staphisagria*

Common Name	Botanical Source
Strophanthus	*Strophanthus kombe* *S.courmonti, S.nicholsoni* *S.gratus, S.emini* *S.sarmentosus, S.hispidus*
Slippery Elm Bark (whole or unpowdered)	*Ulmus fulva* *U.rubra*
Yohimbe Bark	*Pausinystalia yohimbe*

[1]Anon, 1977

Table 2.5 Plants Permitted To Be Sold By A Medical Herbalist

(SI 1977: 2130 Parts II &III)[1]

Common Name	Botanical Source	MD, MDD[2]	Percentage (external use only)
Aconite[3]	*Aconitum napellus,* *A.stoerkianum* *A.uncinatum* var *japonicum* *A.deinorrhizum,* *A.balfourii* *A.chasmanthum* *A.spicatum* *A.lycoctonum*		1.3 %
Adonis vernalis	*Adonis vernalis*	100mg (MD) 300mg (MDD)	
Belladonna	*Atropa belladonna*	50mg (MD)	

Common Name	Botanical Source	MD, MDD[2]	Percentage (external use only)
Herb[2]	*A.acuminata*	150mg (MDD)	
Belladonna Root[2]	*Atropa belladonna* *A.acuminata*	30mg (MD) 90mg (MDD)	
Celandine	*Chelidonium majus*	2g (MD) 6g (MDD)	
Cinchona Bark	*Cinchona calisaya* *C.ledgerana* *C.officinalis* *C.succirubra* *C.micrantha*	250mg (MD) 750mg (MDD)	
Colchicum corm	*Colchicum autumnale*	100mg (MD) 300mg(MDD)	
Conium leaf[2]	*Conium maculatum*		7.0 %
Conium fruits	*Conium maculatum*		7.0 %
Convallaria	*Convallaria majalis*	150mg (MD) 450mg (MDD)	
Ephedra	*Ephedra sinica* *E.equisetina* *E.distachya* *E.intermedia* *E.gerardiana*	600mg (MD) 1800mg (MDD)	
Gelsemium[2]	*Gelsemium sempervirens*	25mg (MD) 75mg (MDD)	
Hyoscyamus	*Hyoscyamus niger* *H.albus* *H.muticus*	100mg (MD) 300mg (MDD)	
Jaborandi[2]	*Pilocarpus jaborandi* *P.microphyllus*		5.0 %

Common Name	Botanical Source	MD, MDD[2]	Percentage (external use only)
Lobelia	*Lobelia inflata*	200mg (MD) 600mg (MDD)	
Poison Oak	*Rhus toxicodendron*		10.0 %
Quebracho	*Aspidosperma quebracho-blanco*	50mg (MD) 150mg (MDD)	
Ragwort	*Senecio jacobaea*		10.0 %
Stramonium	*Datura stramonium* *D.innoxia*	50mg (MD) 150mg (MDD)	

[1]Anon, 1977, Part II and III
[2]MD=Maximum Dose; MDD=Maximum Daily Dose
[3]Listed in Anon, 1983b

2.2.3 Licensed and Unlicensed Herbal Remedies

The medicines legislation discussed under section 2.2.2 focuses on the existence of a medicinal claim in determining whether a herbal product should be considered a medicinal product. It has therefore been relatively easy for manufacturers to market herbal products that to all intent and purpose appear to be a medicine (pharmaceutical presentation, existence of a recommended dose) but which escape the need for licensing because they do not make a medicinal claim. Commonly, products are referred to as a "food" or "dietary" supplement and are controlled under food legislation by MAFF (Ministry of Agriculture, Fisheries and Foods). Indeed, provided herbal products were marketed without reference to medicinal claims the Medicines Control Agency (MCA), the government body responsible for regulating medicinal products, has in the past generally been satisfied that these products were not subject to medicines legislation (Anon, 1982).

Although not legally classified as medicinal products, unlicensed herbal remedies are nevertheless presented to the public as such. Whilst no reference to a medicinal purpose is made on the container labelling and package insert, clever use of shop display units and adjacent literature describing various medical uses are examples of methods used to infer a product's use to the customer. Providing the associated display material and literature do not mention the specific herbal product by name, this is permissible under current advertising regulations (Anon, 1978b). The latter regulations specify the wording that is required to be included on the labelling and package leaflets of licensed herbal remedies, namely:

"A herbal remedy for..."

"Warning: If you think you have [******] consult a registered medical practitioner before taking this product. If you are already receiving medical treatment, tell your doctor that you are also taking this product."

The name of the disease for the treatment of which the herbal product is sold is required to be inserted in [******].

The advertising regulations (Anon, 1978b) also specify the following words may not be included in the labelling of a herbal remedy: Amenorrhoea, Angina, Athersclerosis, Erysipelas, Gallstones, Multiple sclerosis, Osteoarthritis, Phlebitis, Thrombosis, and Ulcer (except where used in the phrase Aphthous ulcer or Mouth ulcer).

It is important to remember that the Medicines Act (MA) and all secondary legislation under it only control activities associated with licensed medicinal products. If a herbal preparation is not considered a medicinal product under the MA, then it remains outside the scope of medicines legislation. There is nothing, therefore, to prevent a book or leaflet from extolling the various medical virtues of a specific herb and a customer then applying this knowledge to self-medicate with a herbal preparation.

The main concern over unlicensed herbal remedies is that they will not have been assessed by the Licensing Authority (LA) and therefore offer no guarantee as to their quality, safety and efficacy. This is of particular relevance when unlicensed remedies are obtained from a pharmacy where consumers associate the purchase of medicines.

Of course there is nothing to prevent a herbal product from actually making medicinal claims without the appropriate licence. This is clearly in breach of the MA and manufacturers of such products risk enforcement action by the LA resulting in possible prosecution.

2.3 Review of Herbal Remedies in the UK

The majority of licensed herbal products available in the UK were marketed prior to the Medicines Act (MA). In September 1971, when the MA came into force, a registration exercise issued all medicinal products already on the market with a Product Licence of Right (PLR) and no scientific assessment was undertaken. In order to be issued with PLRs for their products, pharmaceutical companies simply had to provide details of the products and evidence that the products had been marketed prior to 1971. This procedure applied to all medicinal products including herbal remedies and in total some 39,000 PLRs were granted. It was obvious that at some future date all PLR products (including herbal remedies) would have to be assessed by the LA for their quality, safety and efficacy in the same manner as those products which had applied for a product licence after 1971.

European Community (EC) legislation (Directives 65/65 and 75/319) (Anon, 1965 and Anon, 1975, respectively) required the Review of all PLR products to be completed by May 1990. In the UK this Review commenced in 1975 and was completed by the end of 1990 (Anderson, 1993). A body called the Committee on Review of Medicines (CRM) was established for the duration of the Review to advise the LA on quality, safety and efficacy issues.

When it came to the Review of herbal remedies holding a PLR, the LA agreed to accept bibliographic evidence of efficacy for herbal remedies which were indicated for minor, self-limiting conditions (Anon, 1989d). No evidence would be required from new clinical trials provided the manufacturers agreed to label their products as "a traditional remedy for the symptomatic relief of..." and to include the statement "if symptoms persist consult your doctor". The permitted conditions had to comply with the categories allowed for advertising to the public under The Medicines (Labelling and Advertising to the Public) Regulations 1978 (Anon, 1978b) which gives guidance on medical conditions suitable for self-diagnosis and treatment. The LA considered it inappropriate to relax the requirements for proof of efficacy for herbal remedies indicated for more serious medical conditions. Thus, evidence was required from controlled clinical trials for herbal remedies indicated for conditions considered to be inappropriate for self-diagnosis and treatment. Not surprisingly, in the majority of cases manufacturers agreed to restrict their claims to minor conditions (Anderson, 1993).

Regarding the safety assessment of herbal remedies during the Review, the LA agreed to rely as far as possible on previously published work, such as data supporting use in foodstuffs, topical use, approval by another expert body, and acceptance onto Schedule 1 of the GSL. Obviously, the intended route of administration and recommended dose would have to be comparable. During this safety assessment, a number of herbal ingredients were highlighted as potentially unsafe and their removal from herbal medicines was recommended (e.g. comfrey, sassafras); in other instances the dose of a herbal ingredient was restricted (e.g. berberine in berberis, phytolaccatoxins in pokeroot) (Table 2.6); finally, warning labels were also introduced for products containing herbal ingredients considered potentially harmful in pregnancy (e.g. blue cohosh, broom, juniper) (Anderson, 1993)

Table 2.6 Examples of GSL Herbal Ingredients Restricted By Dose[1]

Herbal Ingredient	Dose Restriction
Berberis	Equivalent of 500mcg berberine MD
Cimicifuga (Black Cohosh)	200mg MD
Blue Flag	600mg MDD
Boldo	1.5g MD
Holy Thistle	1.5g MD
Pokeroot	120mg MD (internal use)
Queen's Delight	320mg MD

[1]Anon, 1984b MD: Maximum Dose MDD: Maximum Daily Dose

During the Review, no concessions could be made regarding the quality assessment of herbal remedies. Guidelines on the requirements of manufacturers to ensure the quality of a herbal medicine were described in the Medicines Act Leaflet (MAL) 39 (now replaced by an EC guideline, Anon 1989c, see section 2.4). These requirements encompassed the usual Good Manufacturing Practice principles but also identified a number of key areas to target such as:

- improving starting material (herbal ingredient) and finished product specifications
- controlling potential contaminants such as pesticides, heavy metals, microbial levels
- generating stability data

In order to achieve many of these new requirements, it was considered essential to rationalise the number of herbal ingredients in any one herbal remedy. Issues affecting the quality assessment of herbal medicines are discussed further in Chapter 3.

2.4 Recent European and UK Legislation

Currently, the MCA regulates medicinal products for human use in accordance with the MA 1968 and the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 SI 3144 (Anon, 1994a). SI 3144 took effect from January 1995 and arose out of the need to implement EC legislation establishing the new EC marketing authorisation procedures. SI 3144 effectively implements into UK legislation the full range of controls set out in Directive 65/65 EEC (Anon, 1965), which apply to 'relevant medicinal products' as defined in SI 3144. The main controls include application requirements and procedures for the grant, variation and renewal of UK licences, requirements in relation to pharmacovigilance, labelling and package leaflets as well as provisions for suspension, compulsory variation or revocation and related enforcement measures. The MA and secondary legislation made under it remain the legal basis for other aspects of medicines control including manufacturer and wholesale dealers' authorisations, controls on sale and supply and controls on promotion.

For herbal remedies, the main impact of the legislation is in the definition of a medicinal product. Article 1 of Directive 65/65 EEC defines a medicinal product as:

"any substance or combination of substances presented for treating, or preventing disease in human beings or animals"
or
"any substance or combination of substances which may be administered to human beings or animals with a view to making diagnosis or to restoring, correcting or modifying physiological functions in human beings or animals is likewise considered a medicinal product".

The first part of the definition describes a product which is medicinal by presentation while the second describes a product which is medicinal by function. Article 1 further specifies that a substance may be of human, animal, vegetable or chemical origin. This definition would clearly include herbal remedies presented as formulated products, irrespective of whether any medicinal claim is made or not. This would have major

implications for the many herbal products previously exempted under the MA (see section 2.2.2).

However, Directive 65/65 EEC (Anon, 1965) also refers to a medicinal product as one that is industrially produced, although this latter phrase is not defined anywhere in EC or UK legislation. SI 3144 (Anon, 1994a) states that a medicinal product is *not* industrially produced if it is a herbal remedy that is sold or supplied under circumstances described by sections 12 (1) and 12 (2) of the MA (Anon, 1968), or by Article 2 of the Medicines (Exemptions from Licences) (Special and Transitional Cases) Order 1971 (Anon, 1971). This effectively preserves the exemptions previously conferred upon herbal remedies prior to implementation of the EC legislation. The Medicines Act Leaflet (MAL) 8 sets out the criteria used by the MCA in determining the medicinal status of a product. A revised edition of MAL 8 (Anon, 1995d) clearly takes into account the new EC definition of a medicinal product, by including reference to a products presentation and intended function. However, MAL 8 also states that it does not affect the current legal status of certain products including exempted herbal remedies and dietary supplements.

The Rules Governing Medicinal Products in the EC are divided into five core volumes plus various supplementary guidelines (Table 2.7). Two guidelines deal specifically with herbal products: The Quality of Herbal Remedies (Anon, 1989c) replaces the former MAL 39 document, and The Manufacture of Herbal Products (Anon, 1992b) is a supplement to EC Volume IV on Good Manufacturing Practice.

Table 2.7 Volumes of EC Rules Governing Medicinal Products

Volume I	EC Directives
Volume II	Notice to Applicants
Volume III	Guidelines on Quality, Safety and Efficacy
Volume IV	Guide to Good Manufacturing Practice
Volume V	Veterinary Practice

2.5 Herbal Remedies in Europe

The advent of the new pan-European marketing authorisation system has raised a number of questions about herbal remedies and their possible transfer to other EC markets. The new systems for marketing authorisations involve three procedures: centralised, mutual recognition (decentralised), and national.

The centralised procedure is mandatory for biotechnology products and optional for high-technology products and medicinal products containing new active substances. The mutual recognition system requires an agreement of assessment between the member states (MSs) involved and will remain optional until January 1 1998 for products requesting authorisation in more than one MS. Thereafter, simultaneous national applications will be possible but the mutual recognition system will be invoked once an authorisation has been granted in the first MS. Existing national procedures will remain for products requesting authorisation in a single MS (Britt, 1995).

Harmonising the authorisation of herbal remedies within the EC is proving to be a difficult task. Both the traditional uses of herbal remedies and their legal status vary between MSs, and the different approaches used by MSs to implement EC Directives 65/65 and 75/319 highlighted these differences.

Clearly, EC harmonisation on what is acceptable for the assessment of quality, safety, and efficacy of herbal remedies is required to enable the mutual recognition system to operate successfully. Within the EC, a Summary of Product Characteristics (SPC) represents the definitive statement on the results of the assessment process of a medicinal product and is binding for all MSs (Keller, 1994). This presents a problem when attempting to establish an SPC for a drug with a traditional use that varies between MSs. Establishing core SPCs for herbal drugs is further complicated by the fact that a herbal drug represents a complex mixture of active components and can exist

in various presentations (different extract types etc.). An important initiative in the harmonisation process has been the formation of ESCOP (European Scientific Co-operative for Phytotherapy), an umbrella organisation representing national associations for phytotherapy. Since 1990, ESCOP has produced three volumes of monographs on herbal drugs drawn from published scientific literature and experience of national delegates (Anon, 1990c). A number of the ESCOP monographs (frangula bark, senna fruit, senna leaf) have been adopted by the EC CPMP (Committee on Proprietary Medicinal Products) as core-SPCs for herbal medicinal products, and could therefore be used in a mutual recognition licence application (Newall et al, 1996). However, difficulties have been encountered in the acceptance of additional ESCOP monographs due to differences of opinion between MSs.

The specific issues involved in the EC harmonisation of quality, safety and efficacy assessment of herbal remedies are discussed respectively in Chapters 3, 4 and 5. In summary, though, it is clear that any harmonisation process rests significantly on achieving a common EC definition of a herbal drug. Safety and efficacy data cannot be comparable between different herbal products (from both within and between MSs) unless the composition of the starting material is comparable. The feasibility of the mutual recognition process and of "generic" herbal preparations within the EC will not be possible until an agreement is reached on common definitions.

2.6 Legislation of Herbal Remedies in the United States (US)

In the US the regulation of food, drugs and medical devices is the responsibility of the Food and Drugs Administration (FDA). The FDA does not currently recognise a separate regulatory status for herbal medicines, and a herbal product which claims to diagnose, treat, prevent or mitigate a disease is considered a drug under the Federal Food, Drug and Cosmetic Act (DeSmet et al, 1993; Hoffman & Leaders, 1996). Consequently, as in the UK, many herbal products are commonly sold as "foods"

including dietary supplements, with information on intended uses available in various books and pamphlets (DeSmet et al, 1993).

With respect to the use of herbs in foods, the well known "Generally Regarded As Safe (GRAS)" list was published in 1958. In 1974, the FDA published a document classifying selected herbs as safe, unsafe, or of undetermined safety, and used this classification as the basis for enforcement actions taken against herbs. The classification was widely criticised within the herbal industry as lacking in a scientific basis (Israelsen, 1996).

It is recognised that the US lags behind many countries in establishing policies and procedures for the evaluation, manufacture, use and regulation of botanical medicines (Hoffman & Leaders, 1996). However, in recent years several developments have signalled a change in the FDA's approach towards botanical medicines. These developments have included the 1994 Dietary Supplement Health and Education Act (DSHEA), with the subsequent establishment of the Commission on Dietary Supplement Labels (CDSL), the establishment of the Office of Alternative Medicine (OAM) in 1991 and of the Office of Dietary Supplement Research (McCaleb, 1996). The mandate of the OAM was to evaluate the most promising "alternative" medical practices (Hoffman & Leaders, 1996). The OAM has funded clinical trial projects to evaluate the role of Chinese herbal remedies, requiring the filing of Investigational New Drug (IND) applications with the FDA. The INDs have been used as somewhat of a test ground for the type of information required by the FDA for botanical products.

There has been considerable disagreement over whether herbal remedies should be regulated differently to dietary food supplements. The mandate of the CDSL was to make recommendations on how herbal medicines should be regulated. It has been suggested that when the CDSL makes its recommendations, estimated for late summer 1997, it will recommend botanical medicines should be treated differently from other dietary supplements, and that a separate category termed herbal remedies should be created for this purpose (McCaleb, 1996). It is hoped that an independent expert panel will be assembled to advise the FDA on the suitability of claims made for botanical

medicines, taking into account traditional usage as well as modern research (McCaleb, 1996). To-date, the FDA has not made any concessions to the nature of the efficacy data required to support a licence application for a botanical product, irrespective of the intended indication(s). The FDA has considered that information such as traditional uses and uncontrolled observations should be used to generate hypotheses tested in controlled clinical trials (Hoffman & Leaders, 1996).

It will be interesting to see how closely US regulatory changes regarding botanical medicines mirror those implemented in the EC, and whether similar problems are encountered in achieving agreement over quality, safety and efficacy issues.

2.7 Discussion

The Medicines Act (MA) exemptions for herbal remedies aimed to remove the burden of obtaining a product licence from herbal practitioners manufacturing their own remedies and from manufacturers of unprocessed, dried herbal material. However, numerous processed herbal remedies also avoid the requirement to hold a product licence by being marketed as food supplements, even though their formulated form and medicinal herb content may suggest an intended medicinal use.

In January 1994, a new statutory instrument SI 1540 (Anon, 1994a) was introduced to implement EC medicines legislation into UK law. Under EC legislation (Anon, 1965) a product is considered to be medicinal by reference to either its presentation or function. The significance of this new definition for herbal remedies is that it includes the presentation of a product in determining its medicinal status, whereas the MA definition refers soley to function. It was hoped that this new definition of a medicinal product would remove the "grey area" that had existed in the UK between medicines and food legislation and into which so many herbal remedies seem to fall. The new definition would have essentially required the many unlicensed but formulated herbal remedies

available in the UK to obtain a product licence, by virtue of their presentation. Not surprisingly significant pressure was lobbied at the government by the BHMA and as a result, the new UK legislation (Anon, 1994a) has been worded to retain the MA exemptions for herbal remedies. In addition whilst MAL 8 (Anon, 1995d) has been revised to take into account the new EC definition of a medicinal product, it also states that the legal status of certain products including herbal remedies remains unchanged.

The wording of both SI 3144 and of MAL8 to preserve the previous licensing exemptions for herbal remedies under the MA, may have solved the immediate problem in the UK but surely represents a temporary solution. The current approach in the UK would appear to be side-stepping the intended objective of the EC definition of a medicinal product. It may be that a separate regulatory category within the EC specifically for herbal remedies is the longterm solution.

The new marketing authorisation systems within the EC seek to promote the free movement of medicinal products from one MS to another, by applying uniform authorisation rules to all MSs. Achieving a pan-European authorisation procedure for herbal remedies is hampered by many issues including the different cultural traditions of member states (MSs) towards herbal remedies, and the variation in MS interpretation of EC legislation at a national level. The concessions made by the UK licensing authority to accommodate the demands of the BHMA are specific to the UK, and may well be considered unacceptable by other MSs. Likewise, decisions made by other MS licensing bodies may be inconsistent with the approach in the UK. It would seem that a new EC regulatory system specifically for herbal remedies and which is independent of existing MS medicines legislation is required.

Many problems have been encountered in trying to establish an EC assessment procedure for the quality, safety and efficacy of herbal remedies, and these are considered in more detail under the discussion sections of Chapters 3, 4, 5 and 7.

3. QUALITY OF HERBAL REMEDIES

As part of the medicines licensing process, all medicinal products are assessed for their quality, safety and efficacy. Of these three, quality plays a central role for quality issues may impact on both the safety and efficacy of a medicinal product. The quality of a herbal medicine is of no lesser importance than that of an allopathic medicine and, indeed, there are additional factors that complicate the quality assessment of herbal medicines.

Before considering these additional factors, it is important to recognise a fundamental difference between allopathic and herbal medicines. The former contain active constituents that are usually well-defined chemical entities, and specific qualitative and quantitative assay procedures are employed to ensure their quality. Herbal medicines, by contrast, contain one or more often several herbal ingredients, each representing a complex mixture of chemical constituents (Newall et al, 1996). Many of the constituents are generic to plants, such as flavonoids, acids, sugars and terpenes, and some difficulty is encountered in establishing both the "actives" in a herbal ingredient and a suitable marker(s) for quality control procedures. In some instances a negative marker is used to ensure the absence of an undesirable constituent, e.g. β-asarone in calamus root. The specific assays utilised for allopathic medicines may therefore be inappropriate for herbal medicines.

When considering the quality of a herbal ingredient, the following aspects must all be taken into consideration: authentication of starting material and natural factors affecting this, adulteration or substitution of herbal ingredients, and contamination of herbal ingredients (both pre- and post-harvesting). The European (EC) guideline on the Quality of Herbal Remedies (Anon, 1989c) states "the consistent quality of products of vegetable origin can only be assured if the starting materials are defined in a rigorous and detailed manner". The guideline provides advice to manufacturers on the required qualitative and quantitative particulars of the botanical constituents, on data required to

ensure control of starting materials, on control tests required to be carried out at an intermediate stage of manufacturing and on the finished product, and on stability tests. With respect to the control of starting materials, the guideline states that a complete monograph must be submitted for each vegetable drug, even if the starting material is a vegetable drug preparation. Information required in the monograph includes the botanical name and authority and common name, site of collection, time of harvesting and stage of growth, treatment received during growth (e.g. pesticides), drying and storage conditions, and assays of constituents of known therapeutic activity. In addition, the guideline recommends that the vegetable drugs must be tested for microbiological quality and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants.

3.1 European (EC) and UK Legislation

EC, and subsequently UK, medicines legislation now clearly defines herbal remedies as medicinal products (see section 2.2). EC legislation has recognised the complexities involved in the quality assurance of a herbal remedy, and has implemented two guidelines to cover this area: Quality of herbal remedies (Anon, 1989c) and Manufacture of herbal products (Anon, 1992b). The former replaces the former UK guideline MAL 39 which contained advice on quality issues for herbal remedies.

Table 3.1 Vegetable Drugs and Preparations Included in the European Pharmacopoeia 1997[1]

Almond Oil	Linseed
Aloe	Liquorice
Aniseed & Anise Oil	Marshmallow
Arachis Oil	Olive Oil
Belladonna	Opium
Cascara	Peru Balsam
Castor Oil	Psyllium
Chamomile Roman	Rhubarb
Cinchona	Senega
Cinnamon	Senna
Clove & Clove Oil	Sesame Oil
Devil's Claw	Soya-Bean Oil
Digitalis	Stramonium
Eucalyptus Oil	Thyme
Fennel (bitter & sweet)	Tragacanth
Gentian	Uva Ursi
Hyoscyamus	Valerian
Ipecacuanha	Witch Hazel
Lemon Oil	
Lime Flower	

[1]Anon, 1997a

The importance of and difficulty in ensuring the quality of herbal medicines is well documented and has been discussed at both EC and International levels (Cranz,1994; Deboyser,1991; Keller,193 & 1994; Phillipson, 1992). EC guidelines on the quality of herbal remedies attempt to ensure the reproducible quality of a herbal remedy. For the new centralised and mutual recognition systems of licensing to work in practice for herbal medicines, there firstly needs to be uniform agreement on the definition of the

starting materials, i.e. the herbal ingredients. The current European Pharmacopoeia (Ph.Eur.) refers to very few botanical drugs used as starting materials in herbal remedies (Table 3.1) (Anon, 1997a). This raises many problems with different national pharmacopoeias referring to, for example, a different botanical source for the same herbal drug (Keller,1994). In addition, the preparation of tinctures and extracts may vary considerably between pharmacopoeial monographs and manufacturers (Keller,1993). In practice, if a pharmacopoeial monograph does not exist for a vegetable drug then a manufacturer must provide its own specification.

ESCOP (European Scientific Co-operative on Phytotherapy) was formed in 1990 to address this problem of an EC definition for a herbal drug. ESCOP aimed to draw up a series of SPCs (Summary of Product Characteristics) for herbal drugs, that are acceptable to all EC member states. By August 1994, it was reported that harmonisation had nearly been reached for herbal laxatives cascara, frangula and senna, but that problems had been encountered for chamomile flowers (Matricariae flos) and valerian root (Valerianae radix) (Keller,1994). To-date, monographs have only been agreed for the herbal laxatives.

3.2 Authentication of Starting Material

In order to ensure the quality of a herbal medicine, the first and most important factor is authentication of starting material, i.e. the herbal ingredient. If this is not achieved any subsequent quality control measures may well be worthless. Full identification of a herbal ingredient involves correct nomenclature, macroscopical and microscopical examination.

Confusingly, a herb may be referred to by four different names: the English common name, transliteration of the herb name, the latinised pharmaceutical name, and the scientific name. For example, the corresponding names for ginseng are: ginseng, ren-shen, Radix ginseng and *Panax ginseng* (But,1993). In addition to *P.ginseng*, the common name ginseng can also apply to *P.quinquefolium* and to *Eleutherococcus*

senticosus. Transliterations and latinised pharmaceutical names can be confusing and, as with common names, difficult to trace back to the original botanical source. It is therefore important that all herbal ingredients are referred to by their binomial Latin name of genus and species.

Macroscopical and microscopical examination with reference to authentic herbarium specimens or recognised textbook descriptions is essential. Manufacturers of herbal medicines may receive herbal ingredients in a comminuted, powdered, or extracted form. Under such circumstances, identification may be impossible and it is therefore essential for the supplier to provide adequate documentation regarding the origin of the herbal material.

Perharic et al (1994) document a case in which hepatitis was associated with the daily use of an Ayurvedic medicine containing Babchi seeds (*Psoralea corylifolia* L.) and Umarda tree bark. Neither herbal ingredients were known to cause hepatitis, although it was not possible to establish the taxonomic identification of Umarda tree meaning further investigation of this ingredient as a possible cause of the hepatitis was not possible.

Misidentification of a Chinese plant included in a slimming preparation was believed to be responsible for serious renal toxicity experienced by some 70 Belgian women, 30 of whom required dialysis or renal transplants (Cosyns et al,1994; Vanhaelen et al,1994). Confusion between *Stephania tetrandra* and the nephrotoxic and potentially carcinogenic plant *Aristolochia fangchi* was linked with the toxicities. The confusion was thought to have arisen because of the similarities in the common Chinese names used for the two plants, Fangji (*S.tetrandra*) and Guang fangji (*A.fangchi*).

Difficulty in establishing the botanical identity of herbal ingredients will obviously hamper any toxicological assessment of a herbal product. Kumana et al (1983) describe four cases of hepatic veno-occlusive disease in Chinese women following their use of an Indian herbal tea for psoriasis. Botanical identification of the toxic ingredient in the tea proved difficult because the tea consisted of chopped leaves, acorns, dates, seeds,

sticks and cones. Unsaturated pyrrolizidine alkaloids, known to be hepatotoxic, were identified in the leaf fraction. Culvenor et al (1986) subsequently confirmed the source of unsaturated pyrrolizidine alkaloids as *Heliotropium lasiocarpum* Fisch and Mey, by germination of seeds found in the leaf fraction and comparison of the resultant plant with a herbarium specimen.

3.3 Batch to Batch Variation

Even when a herbal ingredient has been correctly identified, there are still a number of natural factors that may affect the quality of different batches of a herbal ingredient.

Inter-Intra Species Variation Different species (inter-variation) and sub-species (intra-variation) may differ considerably in their chemical composition. Commercial samples of echinacea, for instance, may refer to one or more of three species (*E.angustifolia, E.pallida, E.purpurea*), which all differ slightly qualitatively and quantitatively in their constituents. Likewise commercial Panax ginseng may contain herbal material from a number of *Panax* species, which are known to vary in their triterpenoid saponin content (Newall et al, 1996). Calamus (*Acorus calamus*) may refer to one or more of the three sub-species (diploid, triploid, tetraploid), which differ significantly in their level of β-asarone, a toxic essential oil component.

Environment Factors such as altitude, climate and growing conditions can affect the quality of a herbal ingredient.

Time of Harvesting The level of constituents in a plant can vary during the growing cycle and even during the course of a day. Optimum conditions for harvesting may therefore be relevant for certain herbal ingredients. It is reported, for example, that *Panax ginseng* and *P.quinquifolius* roots should be harvested between their fourth and sixth year of age to obtain maximum levels of ginsenoside saponins (Anon, 1985). The proanthocyanidin levels in hawthorn leaves were reported to vary between 0.05% and 0.14% in the plant harvested in May and August, respectively.(Hobbs & Foster, 1990).

Plant Part Used Constituents may be subject to both qualitative and quantitative variation between plant parts. It is not uncommon for herbal ingredients to be adulterated with plant parts not normally utilised, or with previously extracted and therefore "exhausted" material. Such practices enable the weight of a batch to be increased at minimal extra cost to the supplier, thereby increasing profits.

Post-Harvesting Factors Storage conditions can affect the quality of a batch and may introduce microbial contamination. In addition, inappropriate drying may result in the loss of thermolabile constituents. Drying studies of hawthorn leaves between 20-150°C concluded optimum drying conditions as less than 20°C or greater than 100°C.(Hobbs & Foster, 1990) Enzymes responsible for a reduction in the flavone content of the leaves are active between the range 20-100°C.

3.4 Identity Tests

Identification of the principle constituents in a herbal ingredient is important from both an efficacy and safety point of view. A herbal ingredient represents a complex mixture of chemical constituents and in view of this, it is difficult to attribute observed pharmacological activities to a single constituent or group of constituents. Nevertheless, for some herbal ingredients the components thought to represent the key "actives" are well defined. Examples include volatile oil and valepotriates in valerian, saponin ginsenosides in *Panax* species, and flavonoids in hawthorn. For these starting materials, identity tests and assays utilising gas liquid chromotography or high pressure liquid chromotography methods can provide qualitative and quantitative methods of quality control. For other herbal ingredients, a broad finger-printing approach is utilised to establish the expected range of constituent types and their relative proportion.

The following case highlights the need for good quality control on starting material, since identification of individual herbal ingredients in a formulated finished product may not be possible. Analysis of a Chinese slimming preparation imported into

Belgium and which resulted in 70 cases of nephrotoxicity, revealed an alkaloid profile different to that expected from the stated herbal ingredients (*Stephania tetrandra* and *Magnolia officinalis*) (Vanherweghem et al, 1993). This analysis did not identify aristolochic acid, characteristic of the suspected toxic adulterant *Aristolochia fangchi* (Vanherweghem et al, 1993). It was subsequently reported that prepurification steps in the initial analysis of the formulated product partially destroyed the aristolochic acid (Vanhaelen et al, 1994). Successful identification of aristolochic acid was finally achieved using Chinese pharmacopoeial analytical methods on samples of the original herb powders imported into Belgium (Vanhaelen et al, 1994).

3.5 Adulteration/Substitution

Many instances of adulteration with both natural substances and synthetic drugs have been documented for herbal products. In any industry where a manufacturer can partially or wholly substitute an expensive ingredient with a less expensive one, this will obviously remain a temptation unless enforceable standards exist to protect against such practices. Adulteration or substitution of a herbal ingredient may impact on the efficacy and/or safety of the resulting herbal remedy. Many of the documented instances of adulteration have come to light because of safety consequences resulting from the adulteration.

3.5.1 Adulteration/Substitution with other Plant Material

Adulteration of a herbal ingredient may be done deliberately, or in error due to a mistake in harvesting. When harvested, all herbal ingredients will contain small amounts of related plant parts or of other plants. These represent unwanted plant contaminants and therefore need to be limited. EC guidelines state that reference samples of the vegetable drug must be available for use in comparative tests (Anon, 1989c).

Commercial sarsaparilla (Liliaceae family) is recognised to be adulterated, most commonly with *Hemidesmus indicus* (unofficially called Indian sarsaparilla) of the Asclepidaceae family (Hobbs, 1988). Apparently the two are easily distinguished: *Hemidesmus indicus* is dark brown with a slight bitter taste and strong smell of vanilla, whereas *Smilax* species are light in colour, have a bland taste and no smell of vanilla. The various official species of sarsaparilla can be distinguished by appearance in their whole form. Although more difficult, a powdered sample can be authenticated by microscopical analysis and reference to microscopic descriptions in the literature (Hobbs, 1988). *Echinacea* species have also reportedly been substituted with *Parthenium integrium* (Prairie Dock) (Anon, 1987).

Digitalis leaves have been adulterated with comfrey leaves (Phillipson,1992). The two can be distinguished microscopically by the appearance of the covering trichomes. Comfrey leaf has also been collected by mistake in place of digitalis. In 1983, a Food and Drugs Administration (FDA) recall of comfrey tea resulted from suspected accidental adulteration of the tea with *Atropa belladonna* leaf (Anon, 1983a). It was suspected that belladonna leaf had accidentally been mixed with the comfrey leaf by an Eastern EC supplier.

Scullcap (*Scutellaria* species) is an EC herb that has traditionally been used in the treatment of nervous and tension disorders. There have been a number of documented cases of hepatitis associated with multi-ingredient herbal preparations all containing scullcap (Harvey & Colin-Jones,1981; MacGregor et al,1989). At the time of documenting these cases, there was no strong evidence to implicate scullcap as the toxic component: the known phytochemistry of *Scutellaria* is limited to flavonoids, volatile oils and tannins (Newall et al, 1996). Certainly no obviously toxic constituents have been reported. However, it is now well recognised that commercial scullcap is adulterated with a *Teucrium* species, notably *Teucrium canadense*. Little has been documented on the phytochemistry or pharmacology of *T.canadense*, although diterpenoid constituents have been reported (Bruno et al, 1989). Interestingly, diterpenoids are thought to represent the hepatotoxic constituents in the related species *T.chamaedrys* (germander) (Loeper et al, 1993). Germander has been associated with a

number of reports of hepatitis in France and was prohibited from sale by the French Department of Health in April 1992 (Mostefa-Kara et al,1992). Whether *T.canadense*, and presumably commercial scullcap, presents the same hepatotoxic risk as germander has not been established but is obviously under question. Huxtable (1992) refers to two cases of scullcap poisoning, one fatal, from Norway in which it is unknown if the toxicity was due to *Scutellaria*, *Teucrium*, or some other herb.

Hawthorn leaves and flowers may be adulterated with those from members of the *Prunus* genus, or admixtures of various *Crataegus* species may be presented (Hobbs & Foster, 1990). Macroscopical examination can easily identify adulterants, but requires the whole plant material.

3.5.2 Adulteration with Synthetic Drugs

Numerous reports of adulteration of Asian medicines, notably Chinese preparations, with allopathic medicines have been documented and have recently been summarised by DeSmet et al (1992). The labelling of adulterated herbal remedies usually makes no reference to their prescription-only, and in some cases banned, medicinal ingredients. Recommended doses of the herbal preparations often result in therapeutic doses of the undeclared, allopathic medicines. Western clinicians are usually alerted to the use of an adulterated herbal preparation by a dramatic improvement in a patient's clinical status, or by unexplained side-effects or withdrawal symptoms. Occasional instances of herbal preparations including reference to allopathic constituents on the labelling have been documented. Kshirsagar (1993) described a traditionally named Ayurvedic product, Vendana Nigraha Rasa, which contained 530mg aspirin and 100mg paracetamol. Despite the labelling referring to these constituents, the product had been purchased by an educated patient who had been told to avoid aspirin, and who had assumed the Ayurvedic medicine would not contain any Western drugs. O'Driscoll et al (1992) reported the supply by a Chinese herbalist of the potent topical steroid flucinolone acetonide 0.025% for use on the face of a 5 year old Chinese boy.

A single Chinese herbal preparation for rheumatoid arthritis, named Chuifong Toukuwan (CT), has been responsible for many reports of adulteration in countries including Australia, Belgium, Holland, UK and USA.

Two reports of agranulocytosis following the use of CT in the United States and Australia have been documented (Ries & Sahud, 1975; Brooks & Lowenthal, 1977). The preparations were sold for use in rheumatoid arthritis and were found to contain aminopyrine and phenylbutazone, both known to cause agranulocytosis. In addition, the preparation available in Australia contained phenacetin and mercuric sulphide (Brooks & Lowenthal,1977). In 1979 CT was also reported in use in the UK, although the patient had obtained it from friends in Holland where CT was receiving much attention as an effective remedy for arthritis (Forster et al,1979). Analysis of the CT available in Holland revealed dexamethasone and indomethacin as adulterants. In 1982, a variety of side-effects were experienced by 13 rheumatoid arthritis patients in the USA who had obtained CT by mail order from Hong Kong (Goldman,1991). Analysis of this particular batch revealed indomethacin, prednisone and lead. In 1994, a further report of CT use was reported from Belgium (Stricht et al,1994). On this occasion, analysis revealed the new presence of diclofenic and mefenamic acids together with previously identified hydrochlorothiazide, indomethacin, dexamethasone and diazepam.

No indication of the allopathic drug content was mentioned on the labelling or packaging of these CT preparations. Not only, therefore, does CT contain undeclared, prescription-only medicines, but also the medicines added vary between batches. Forster et al's paper stimulated letters reporting other adulterated Chinese herbal preparations in Holland (Offerhaus et al,1979) and Germany (Kimbel,1979). Newton (1979) reported a number of patients in the UK with rheumatoid arthritis who were using a Chinese herbal remedy obtained directly from Hong Kong. The pills had not been analysed, but the speed of remission of the patients' symptoms was reportedly highly indicative of steroid and/or anti-inflammatory constituents.

Chinese remedies analysed by a surveillance project carried out at the Medical Toxicology Unit (MTU) at Guy's Hospital (formerly the National Poisons Unit) have

been found to contain various allopathic drugs including aspirin, phenacetin, and phenobarbitone (Shaw et al, 1996).

Anyanwu & Okonkwo (1981) discuss three case histories involving oesophageal strictures induced by herbal preparations bought from traditional healers in Nigeria. Product samples were available in two of the cases and analyses revealed a toxic mixture of chemicals and musculotropic alkaloids. The authors commented that the oesophageal strictures were probably due to a combination of the musculotropic and corrosive effects of the preparations. The labelling of the preparations did not indicate the nature of the ingredients.

Fewer instances of non-Asian medicines adulterated with synthetic medicines have been reported. Huxtable (1990) described an instance of a Californian herbal remedy used by two patients in Switzerland which claimed to contain no Western medicine and no cortisone. The product was found to contain betamethasone after one patient developed Cushing's syndrome and the other adrenal cortisol suppression. A herbal remedy marketed in Las Vegas for arthritis and high blood pressure was found to contain indomethacin, hydrochlorothiazide, and diazepam (Anon, 1984a).

3.5.3 Adulteration with Toxic Metals

Toxic metal contamination has been reported for many ethnic remedies but in particular for Asian medicines, and many of these cases have been summarised by DeSmet et al (1992). Ayurvedic medicine is a traditional form of Indian healing utilising mixtures of crude herbals, minerals and heavy metals.

Tay et al (1975) described 74 cases of arsenic poisoning in Singapore, noted over a 15 month period. 64% of the chronic poisoning cases (70% of total) were attributed to ingestion of a single local anti-asthmatic preparation containing 12,000ppm of inorganic arsenic sulphide. Another 28 brands of Chinese herbal preparations, mostly

imported, were subsequently identified containing inorganic arsenic levels ranging from 25-107,000 ppm.

Aslam et al (1979) surveyed various Asian medicines and cosmetics in the Birmingham area, and reported contamination with heavy metals such as lead, arsenic and mercury. Other metals such as iron, copper and zinc were also identified. In one traditional remedy, the source of lead was from the spoon onto which a paste was applied and allowed to dry.

Kew et al (1993) reported two cases of heavy metal intoxication in Asian men who had ingested traditional Indian remedies for eczema , prepared by a visiting hakim. The preparations dispensed by the hakim were found to contain toxic amounts of inorganic arsenic and mercury. Dolan et al (1991) described a case of lead poisoning in a Pakistani man who had taken three traditional Asian medicines for impotence. One of the three preparations was found to have a very high lead content. Mitchell-Heggs et al (1990) describe a case of lead and arsenic intoxication in a Korean woman living in the UK. The woman had obtained a traditional remedy for haemorrhoids whilst visiting Korea. Analysis of the remedy, small hard pellets, revealed high levels of arsenic and lead. Pontifex et al (1985) reported a case of lead poisoning in a diabetic Asian Indian man, who had obtained an Ayurvedic remedy for diabetes whilst visiting India.

The MTU surveillance project reported toxic metal contamination (arsenic, lead, mercury) of Chinese and Indian herbal remedies (Shaw et al, 1996).

Schaumburg et al (1992) reported two cases of alopecia and sensory polyneuropathy resulting from thallium intoxication subsequent to ingestion of a Chinese herbal remedy.

Many authors have reported concerns over the traditional cosmetic use of surma, a fine powder applied to the conjunctival surfaces of the eyelid in Asian children. The surma often contain a high level of lead and their use has been associated with high blood lead concentrations (Aulfat et al,1978; Aslam et al,1980). Lead from the surma is thought to

enter the bloodstream by lacrimation or by transference via the fingers to the mouth (Aslam et al,1980).

3.6 Contamination

Herbal ingredients should be of a high quality and free from insect, other animal matter and excreta. Obviously, it is not possible to remove completely all contaminants and therefore specifications are required to limit them.

3.6.1 Microbial Organisms

Aerobic bacteria and fungi are normally present in plant material and may increase due to faulty growing, harvesting, storage or processing. In the past, results of contamination studies on herbal drugs were often compared to the FIP (Federation Internationale Pharmaceutique) requirements for non-sterile medicines (DeSmet et al,1992). However, these requirements applied to finished medicinal products and therefore did not take into account either the natural microbial contamination or the raw status of herbal drugs. Not surprisingly, many herbal drugs were reported with a microbial count exceeding the FIP limits (DeSmet et al, 1992). Current EC requirements for the microbial quality of pharmaceutical preparations (Anon, 1997a) include levels specifically for herbal remedies (Table 3.2). It has been suggested that rather than total microbial counts (as specified in the EC requirements), it is more useful to know levels of pathogenic organisms including *Enterobacter*, *Enterococcus*, *Clostridium*, *Pseudomonas*, *Shigella* and *Streptococcus*, which have all been shown to contaminate herbal ingredients (DeSmet et al, 1992). It should also be taken into account that extraction and formulation procedures may result in a reduced microbial count in the finished product.

Table 3.2 EC Microbiological Limits for Herbal Remedies[1]

Herbal remedies to which boiling water is added before use:
Total viable aerobic count:
Not more than 10^7 aerobic bacteria per g/ml
Not more than 10^5 fungi per g/ml
Not more than 10^2 *Escherichia coli* per g/ml
Other herbal remedies:
Total viable aerobic count:
Not more than 10^5 aerobic bacteria per g/ml
Not more than 10^4 fungi per g/ml
Not more than 10^3 enterobacteria and certain other gram-negative bacteria per g/ml
Absence of *Escherichia coli* in 1g or 1ml
Absence of *Salmonella* in 10g or 10ml

[1] Anon, 1997a

3.6.2 Bacterial and Fungal Toxins

Gastro-intestinal exposure of healthy individuals to fairly high levels of bacterial contamination, even pathogenic bacteria, may not result in a clinical illness (DeSmet et al, 1992). However, heavy bacterial contamination of a herbal drug intended for use in a parenteral preparation is of particular concern because of the risk of bacterial endotoxins. DeSmet et al (1992) list instances where German phytotherapeutic parenterals have been shown to be contaminated with bacterial endotoxins. It would seem wise for all parenteral phytotherapeutic preparations to be screened for the absence of pyrogens.

Inappropriate drying or poor storage of herbal material in humid conditions may result in yeast and mould contamination. The presence of mycotoxin-producing fungi is of particular concern and a wide variety of mycotoxins has been identified from feeds and foodstuffs (DeSmet et al, 1992). Aflatoxins, produced by *Aspergillus* strains, are mutagenic and carcinogenic and are therefore considered especially dangerous. Relying on a total fungal count may not be an appropriate indicator of mycotoxin contamination, since decontamination may reduce a fungal count without destroying the already formed toxins (DeSmet et al, 1992).

3.6.3 Pesticides and Fumigants

The dangers associated with many pesticides have been recognised and many countries have now introduced restrictive regulations on their use. There is a number of reasons why herbal material can still be contaminated with pesticides including that a country of origin does not operate the same restrictive use of pesticides, that adjacent land has been heavily sprayed, the persistence of earlier use of pesticides, and that insufficient time has been allowed between pesticide spraying and harvesting. Residues of chlorinated hydrocarbons including DDT are reported to commonly occur in crude herbal material (DeSmet et al, 1992) Other documented pesticide residues in herbal material include organophosphates, carbamates or polychlorinated biphenyls. The European Pharmacopoeia (Ph.Eur.) includes clear, but nevertheless non-mandatory, limits for pesticide residues in herbal material intended for medicinal use, together with recommendations on suitable assay methods for determining pesticide residues (Anon, 1997a). A food regulation (HMVO) does exist which describes maximum permitted pesticide residue levels for non-medicinal tea and tea-like products (DeSmet et al, 1992). Studies of pesticide residue levels in crude botanical drugs have reported many herbs to be outside the HMVO limits. However, it has also been suggested more appropriate to analyse the toxicological risk of pesticide residue levels in medicinal herbs by calculating the daily intake of the residue and comparing this to the WHO/FAO acceptable daily intake value (DeSmet et al, 1992) Pesticide residue

contamination has been shown to be reduced by both aqueous (boiling) and ethanolic extractions (DeSmet et al, 1992). It is therefore essential that an analysis of pesticide residue contamination is performed on both the crude herbal material and on the finished herbal product.

Residues in botanical drugs may also result from the use of fumigant agents such as ethylene oxide, methyl bromide and phosphine. It has been reported that ethylene oxide may alter the phytochemical composition of a herb, forming new constituents with unknown pharmacological and toxicological properties (DeSmet et al, 1992). Toxicological risks associated with exposure to these substances means their use is no longer permitted in the EC. The use of ethylene oxide is only acceptable when considered absolutely necessary, with an upper limit set at 1ppm (Anon, 1993d).

3.6.4 Radioactivity

The Chernobyl disaster in 1986 stimulated considerable research into the toxicological risk of botanical material exposed to radioactive fallout. There are no official limits defined for permitted levels of radioactivity in medicinal herbs. Existing EC regulations for fresh foods set a maximum permitted level of 600Bq/kg for Cs136/137. Reports of crude herbal drugs destined for the West German market with Cs136/137 levels in excess of 600Bq/kg have been documented (DeSmet et al, 1992). Whether it is appropriate to apply the Cs136/137 limit for fresh foods to medicinal herbs is debatable: foods would be consumed in greater quantities, and some studies have reported an incomplete passage of radioactivity during extraction procedures (DeSmet et al, 1992).

3.6.5 Environmental Pollution

The environmental conditions under which herbal material is grown may provide a source of contamination. Toxic metal contamination of herbal material may result from environmental pollution, and will vary more in herbs grown under wild rather than cultivated conditions. The ability of marine plants to accumulate heavy metals and other

toxic elements is recognised (Newall et al, 1996). Brown seaweed (*Fucus* species), commonly referred to as kelp or bladderwrack, is a common constituent of herbal remedies traditionally used for obesity and goitre. Elevated urinary arsenic concentrations have been associated with the ingestion of kelp tablets (Newall et al, 1996). With respect to kelp preparations, in the UK provisional limits have been set of 75ug for the acceptable daily intake of total heavy metals and toxic elements including arsenic, and 0.5mg for daily iodine intake (Personal communication, Anderson LA).

Current EC guidelines (Anon, 1989c) require vegetable drugs to be tested for toxic metals but do not specify any acceptable limits. Metals that have been taken into consideration in the quality assurance of herbal material are arsenic, cadmium, lead, mercury and less commonly thallium. As with pesticide residues, the toxicological risk of toxic metal levels in botanical drugs is best assessed by calculating average weekly metal intakes and comparing the results with the provisional weekly tolerable intake (PWTI) values established for toxic metals by the FAO/WHO (Table 3.3) (DeSmet et al, 1992).

Table 3.3 PWTI Values for Toxic Metals

Metal	**PWTI value (mcg/kg/week)**
Arsenic (inorganic)	15[a]
Cadmium	7
Lead	50[b]
Mercury	5[c]

a Does not refer to organoarsenicals which are naturally occurring and considerably less toxic
b For children, 25mcg/kg/week
c For methyl mercury, maximum of 3.3mcg/kg/week

Factors that need to be considered when using the PTWI values for a toxicological assessment of toxic metals in herbal drugs are the percentage of a PTWI contributed by normal dietary intake, narrow safety margins between PTWI values and a clinically toxic level, whether PTWI values only apply to healthy adults, and potentially low extraction rates of toxic metals during processing (DeSmet et al, 1992).

The mean dietary intake of toxic metals has been studied in a number of countries and found to constitute a considerable percentage of the official tolerable intake value. For example, in the UK dietary intake of cadmium and lead represents respectively 33% and 27% of the official tolerable values (DeSmet et al, 1992). When considering the arsenic content of a herbal drug, it is important to distinguish between organoarsenic and inorganic arsenic. The latter is considerably more toxic. Organoarsenical intakes of up to 50 mcg/kg/day have reportedly not resulted in any ill effects, compared to the daily tolerable intake for inorganic arsenic of 2.14mcg/kg/day (adjusted from the PTWI value) (DeSmet et al, 1992). It has also been reported that in the UK, 100% of the tolerable arsenic intake is ingested from dietary sources (DeSmet et al, 1992). However, the daily exposure to inorganic arsenic in the UK is known to be very low.

3.6.6 Ash Values

Incineration of a herbal ingredient produces ash which constitutes inorganic matter. Treatment of the ash with hydrochloric acid results in acid-insoluble ash which consists mainly of silica and which may be used as a measure of soil present. Limits may be set for ash and acid-insoluble ash levels. Current EC guidelines require all vegetable drug starting materials to comply with a pharmacopoeial monograph which would include acceptable limits for ash and acid-insoluble ash. If no pharmacopoeial monograph exists for a vegetable drug, then the manufacturer must justify the ash limits set in its own specification for the drug.

3.7 Control and Stability Tests

EC guidelines include the need for control tests (intermediate and on the finished product) and stability tests for herbal medicines (Anon 1989c; Anon, 1992b). Control tests must be able to determine qualitatively and quantitatively the composition of the active ingredients or of designated markers if the active ingredients are unknown. The importance in determining stability of a whole herbal preparation rather than specific active constituents is recognised by the EC guidelines. Fingerprint chromatograms are suggested as a means of ensuring the stability of all the components in a herbal preparation. Difficulties obviously arise in developing control and stability tests for a herbal preparation containing a number of herbal ingredients which have constituents in common. In such circumstances, the onus is on the manufacturer to justify the nature of the control and stability tests used.

3.8 Discussion

Ensuring the quality of a herbal remedy is central to ensuring its safety and efficacy. All medicinal products are required to comply with certain criteria set out under EC and national legislation to ensure their suitable quality. However, herbal medicines present many unique difficulties with respect to quality control requirements such as starting material authentication, contamination limits, and intermediate, finished product and stability control tests. The principle reason for this is that a herbal starting material represents a complex mixture of chemical constituents rather than a well-defined chemical entity. Rigorous authentication of a herbal starting material is recognised in EC guidelines as paramount although in practice, this may be difficult to achieve. Details such as geographical site of collection, harvesting time and stage of growth may not always be available or, if provided, easy to confirm.

Authentication of a herbal drug versus a recognised monograph providing macroscopical and microscopical details is of obvious importance. Difficulties arise when a manufacturer receives herbal material in a comminuted or powdered form or as

a prepared extract. The EC guideline on the manufacture of herbal medicinal products (Anon, 1992b) acknowledges the importance of staff well qualified in the handling of herbal material being involved in the manufacturing process. The ability to identify erroneous or adulterated herbal material is essential in ensuring the subsequent quality of a herbal preparation. Difficulties also arise when no common specification exists for a herbal drug, thus leading to potential variation between manufacturers and thus preparations. It has proven difficult to establish EC-wide pharmacopoeial definitions of herbal drugs. Progress is being made under the ESCOP organisation, but to-date definitions have been reached for only for a limited number of herbal drugs. In view of this, achieving EC definitions for extracts may not be feasible, further reducing the possibility of "generic" herbal preparations within the EC.

In addition to starting material authentication, EC guidelines on the quality (Anon, 1989c) and manufacture (Anon, 1992b) of herbal remedies recognise the need for control of adulterants, microbial contamination, ash values, radioactivity, pesticide and fumigant residues, and heavy/toxic metals. The guidelines do not, however, set specific limits for many of these factors and what is considered acceptable is therefore a matter of judgement of individual manufacturers and national licensing bodies. The onus is clearly on the manufacturer to justify the tests which have been carried out and the limits set. Clearly, there is room for variation between the licensing bodies of different EC member states over acceptable tests and limits applied for a herbal starting material and finished product.

Medicines legislation has had to adapt to the specific requirements of herbal medicinal products and despite the difficulties in implementing all of the requirements and in achieving EC harmonisation, licensed herbal medicines do provide an assurance over their quality. Perhaps of more concern is the quality of the many unlicensed herbal remedies available in the UK. A recent initiative by the British Herbal Medicine Association (BHMA) will hopefully represent an important step forward in ensuring the quality of unlicensed herbal remedies manufactured by BHMA members. The BHMA recognises that whilst it has fought hard to preserve the exemptions for herbal remedies under the Medicines Act, it is also important to ensure the quality, safety and efficacy

of these products. The BHMA has therefore proposed a Code to its members outlining a framework of good practice with respect to the manufacture of herbal remedies (Perfitt, 1996). The Code reportedly applies the same legal constraints on quality, manufacture and labelling for licensed medicines to herbal remedies exempted under sections 12 and 56 of the Medicines Act. With respect to quality, the BHMA Code requires compliance of starting materials with the European Pharmacopoeia, British Pharmacopoeia, British Herbal Pharmacopoeia or Chinese Pharmacopoeia as appropriate. In addition, the Code prohibits heavy metals, synthetic medicinal substances and substances from endangered animal species as ingredients of a herbal remedy. Enforcement is key to the success of a voluntary Code of Practice and the BHMA has undertaken to refer to the MCA any serious breaches which involve safety issues. How this will work in practice will have to be seen but it would seem in the interests of BHMA members for BHMA status to be associated with herbal products of a reliable quality.

In addition to EC herbal remedies exempted from controls of the Medicines Act, there is a growing concern over the increasing number of non-EC herbal remedies available in the UK. The diverse cultural mix within Western countries is introducing many traditional healthcare systems to a Western audience. Many of these systems are inherently unsafe in view of the substances that are used in the remedies.

Instances of adulteration with toxic metals and/or allopathic drugs have been reported for traditional Chinese medicines (TCM) and for Ayurvedic remedies. Chinese remedies may either be in the form of a combination of loose herbs for use as a decoction, or be presented as formulated products. The latter would appear to be aimed at a Western market, with remedies presented in brightly coloured boxes and often containing undeclared allopathic drugs to ensure a desirable therapeutic response. Ries & Sahud (1975) and Brooks & Lowenthal (1977) noted that instances of agranulocytosis following the use of adulterated Chinese medicines did not involve the local Chinese community. They suggested that the adulterated products were perhaps prepared specifically for the Western market. Of additional concern, Brooks & Lowenthal (1977) observed different adulterants added to different batches of the same product. However, Shaw et al (1996) noted that in China it is acceptable for Chinese

Patent Medicines (formulated forms of Chinese herbal medicines) to contain allopathic drugs and that the Chinese Pharmacopoeia even contains some formulae which include mercury, arsenic or other trace elements. As with EC herbal remedies, authentication of the herbal material present in TCM is essential. Over 300 Chinese medicinal herbs are imported from China into the UK, and a survey of herbal materials obtained from 10 TCM suppliers in the UK revealed some doubt over the identity of "authenticated" samples (Yu et al, 1995). The establishment of a reference collection of TCM material at The Royal Botanic Gardens in Kew (Shaw et al, 1996) will hopefully assist importers and manufacturers in their authentication of imported plant material.

Similarly, many Ayurvedic remedies traditionally contain toxic metals, such as arsenic, lead and mercury, as constituents. Attempting to halt the use of these traditional remedies by immigrant populations is probably impossible. Most sizeable Asian communities now have three or four resident hakims, and an unknown number regularly visit Britain from abroad to practise for a few weeks (Kew et al,1993). Most hakims are medically unqualified and their services are widely advertised in Asian newspapers in Britain (Kew et al,1993). Many immigrants will turn to their traditional system of medicine before contemplating Western methods. In the various documented reports of heavy metal poisoning following the use of Ayurvedic medicines, many of the patients obtained the remedies from local hakims or whilst visiting their native country. A recent report described the presence of allopathic drugs in a "herbal" hayfever remedy (Raman & Jamal, 1997). The remedy, which consisted of tablets and a powder, was purchased in India by an Indian woman usually resident in the UK. Analysis revealed the presence of chlordiazepoxide in the tablets, and of chlorpheniramine, theophylline and probably prednisolone in the powder.

Preventing the personal use of Chinese and Indian herbal remedies is not feasible. Educating consumers on the potential health risks associated with these remedies would seem the best approach.

Factors affecting the quality control of herbal remedies are further discussed in Chapter 7.

4. SAFETY OF HERBAL REMEDIES

4.1 General considerations

The safety of all medicines is of the utmost importance. The majority of medicines contain pharmacologically active substances and therefore cannot be totally devoid from potential side-effects. As part of the licensing process, all medicinal products are assessed for their safety using a risk versus benefit analogy. Hence a serious side-effect profile is more likely to be permitted for a medicine used in a life-threatening condition than for one indicated for a lesser ailment. In addition to the intended indications for a medicine, the frequency of a serious side-effect is also important. For example, Steven's Johnson Syndrome (SJS) is a potentially fatal side-effect associated with certain commonly used antibiotics such as amoxycillin (Anon, 1996a). However, the frequency in occurrence of SJS is considered low enough to permit the general use of amoxycillin without exposing patients to an unacceptable risk. The risk versus benefit assessment is extremely important and must be constantly reviewed throughout the lifetime of a medicine. A favourable risk/benefit ratio at the time of licensing based on safety data obtained from clinical trials, does not mean that the balance will remain the same once the medicine is prescribed within the general population. In the United Kingdom (UK), this constant review is carried out by the Medicines Control Agency (MCA) using a voluntary spontaneous adverse reaction reporting system known as the "yellow card system". Data on suspected adverse reactions are supplied to the MCA by doctors (GPs and hospital), dentists, coroners, and more recently pharmacists. In addition, market authorisation holders (the pharmaceutical companies) have a statutory obligation under the terms of their product licence to supply the MCA with any information on suspected adverse reactions to their products (Anderson, 1997).

As with all forms of self-treatment, the use of herbal remedies presents a potential risk to human health. Self-administration of any therapy in preference to orthodox treatment

may delay a patient seeking qualified advice, or cause a patient to abandon conventional treatment without first seeking qualified advice. If orthodox treatment is abandoned in favour of a therapy of unproven efficacy or administered by an unqualified practitioner, this obviously presents further health risks to the patient. This issue is discussed in Chapter 5 which considers the efficacy of herbal remedies.

A herbal remedy is similar to a conventional medicine in that it also contains pharmacologically active substances and is therefore capable of producing side-effects. Some of the side-effects associated with herbal remedies are predictable from the known pharmacological activity of the constituents (e.g. anthraquinone glycosides) whilst others may relate to the inherent toxicological risk of the constituents (see Section 4.2). In addition, there are other factors specific to herbal remedies that present a potential risk to human health. In Chapter 3, the quality of herbal remedies is discussed. Poor quality of a herbal remedy may impact significantly upon the risk the remedy presents to human health. Indeed, instances of quality errors very often only come to light after they have precipitated some form of human toxicity. Many examples of herbal remedies contaminated with conventional drugs, toxic metals or toxic plants have been reported in the literature and these are discussed in Chapter 3. The solution to these additional safety risks would appear to be in requiring the licensing of all herbal remedies as medicines, thereby ensuring a thorough assessment of their quality, safety and efficacy. However, in reality, this solution is not practical and moreover not enforceable under medicines law. For many non-Western cultures, herbal remedies are one of many forms of healthcare that have been used for centuries and which represent an intrinsic part of the cultural makeup. The considerable cultural diversity that now exists in the UK means that we are observing toxicities specifically associated with traditional forms of healthcare. Ayurvedic medicine, for example, is a traditional form of Indian healthcare that utilises toxic metals in the remedies. The most feasible solution to safety risks presented by traditional forms of healthcare is probably in the education of individuals who trust and use the remedies.

The extensive traditional use of plants as medicines has enabled those medicines with acute and obvious signs of toxicity to be well recognised and their use avoided.

However, the premise that traditional use of a plant for perhaps many hundreds of years establishes its safety does not necessarily hold true. The more subtle and chronic forms of toxicity, such as carcinogenicity, mutagenicity, and hepatotoxicity, may well have been overlooked by previous generations and it is these types of toxicities that are of most concern when assessing the safety of herbal remedies.

This chapter will discuss the safety hazards relevant to European (EC) herbs which are commonly used as ingredients of herbal remedies available in the UK. There are many plants native to the UK that are recognised as poisonous (Cooper & Johnson, 1984; Frohne & Pfander, 1984), but the majority are either ornamental or do not have a traditional medicinal use. However certain medicinal plants are recognised as potentially toxic, and legislation drawn up under the Medicines Act acknowledged particularly hazardous herbs and restricted their use to Prescription Only Medicines (POM) (Anon, 1983b). In addition, certain non-POM plants are restricted to Pharmacy Only sale or to supply only via a medical herbalist (Anon, 1977). Chapter 2 discusses the medicines legislation that affects herbal remedies.

Some herbs represent a potential health hazard because they contain constituents that are toxicologically significant (DeSmet et al, 1992 & 1993). Section 4.2 considers such constituents and the herbs in which they occur in significant levels. Some of the herbs considered within this section, such as comfrey and sassafras, are no longer permitted in licensed herbal medicines in the UK because of the potential health risk that they present. Essential oils represent an important phytochemical component of many herbs from both a safety and efficacy standpoint. Some constituents of essential oils are associated with a potential safety risk and these are also discussed under Section 4.2. Adverse effects unrelated to poor quality issues have been reported for herbal remedies and are discussed under Section 4.3. Side-effects may be associated with the known pharmacological actions of the herb or with toxicological properties associated with specific constituents of the herb. As with conventional medicines, potential interactions between herbal remedies and other conventional medicines can be postulated and are discussed under Section 4.4. Unfortunately, these potential interactions are primarily based on the known pharmacological properties of a herb rather than on documented

clinical cases. Occasional reports of interactions between herbal and conventional medicines have been reported in the scientific literature, but overall clinical information is very sparse. A lack of reports does not, however, mean that interactions do not occur and it is important for doctors to be aware of any herbal remedies that their patients may be self-administering. The use of medicines during pregnancy is a highly sensitive area and the suitability of using herbal remedies during pregnancy is discussed under Section 4.5. Finally, Section 4.6 considers safety issues associated specifically with herbal teas.

4.2 Herbal Ingredients with Toxicologically Significant Constituents

Some constituents of herbal ingredients are associated with a specific toxicological risk, irrespective of whether they contribute to the pharmacological activity of the herb. Table 4.1 lists such constituents of EC herbal ingredients, grouped by their constituent type, together with their toxicological effect and herbal source.

Table 4.1 Toxicologically Significant Constituents in Herbal Remedies

Constituent Type	Constituent	Toxicological Effect	Example of Herbal Source
Alkaloid			
Isoquinoline	Sanguinarine, Chelerythrine, Protopine	Carcinogenicity reported for some BA[1]	Bloodroot, Prickly Ash
Pyrrolizidine	Symphytine Senecionine Senkirkine Lycopsamine	} Hepatotoxic, } carcinogenic, } genotoxic }	Comfrey Liferoot Coltsfoot Borage

Constituent Type	**Constituent**	**Toxicological Effect**	**Example of Herbal Source**
Quinolizidine	Sparteine	Cardiotoxic	Broom
Anthraquinone	Cascarosides, Sennosides Hypericin	GI mucosal stimulant Photosensitivity	Cascara, Senna St. John's Wort
Cyanogenetic Glycoside	Amygdalin	Cyanide poisoning	Apricot
Diterpene	Stillingia factors (esters) Furano-diterpenes	Severe mucous membrane irritant Hepatotoxic	Queen's Delight *Teucrium* species
Essential Oil *Alkenylbenzene Derivative*	Anethole (*trans*) Apiole β-Asarone Estragole Myristicin Safrole	Oestrogenic (weak) Toxic, Abortifacient Carcinogenic, genotoxic Carcinogenic Psychoactive Carcinogenic, genotoxic	Anise, Fennel Star Anise Parsley, Dill Calamus Basil Fennel Tarragon Nutmeg Sassafras
Monoterpene	Camphor Pulegone Thujone	Toxic, convulsive Irritant, hepatotoxic Toxic, convulsive	Rosemary, Sage, Yarrow Pennyroyal, Ground Ivy Tansy
Sesquiterpene	Anthecotulid,	Allergenic	Chamomile

Constituent Type	Constituent	Toxicological Effect	Example of Herbal Source
Lactone	Nobilin		
	Parthenolide	Allergenic, (?) cytotoxic	Feverfew
	Alantolactone	Allergenic	Elecampane
Furanocoumarin	Bergapten	Phototoxic	Angelica
	Xanthotoxin		Celery
Lignan	NDGA[2]	Hepatotoxic	Chaparral
Protein			
Lectin	LI, LII, LIII	}Haemaggluting,	Mistletoe
	Pokeweed mitogen	} mitogenic	Pokeroot
Viscotoxin	Viscotoxins A_2, A_3, B	Cardiotoxic, Cytotoxic	Mistletoe
Saponin	Aescin	Nephrotoxic	Horsechestnut
	Phytolaccosides	GI irritant, Haemolytic	Pokeroot

[1] BA = Benzophenanthridine Alkaloids
[2] NDGA = Nordihydroguaiaretic Acid

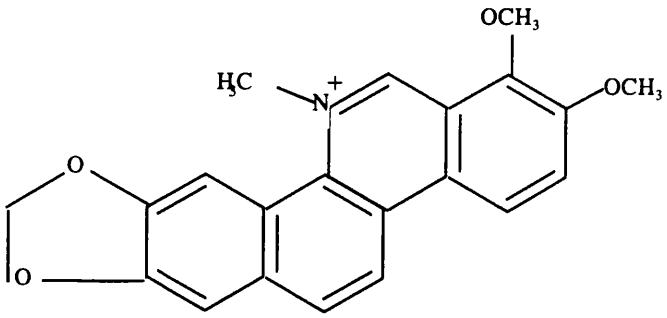
4.2.1 Benzophenanthridine Alkaloids

4.2.1.1 Chemistry, Occurrence and Toxicity

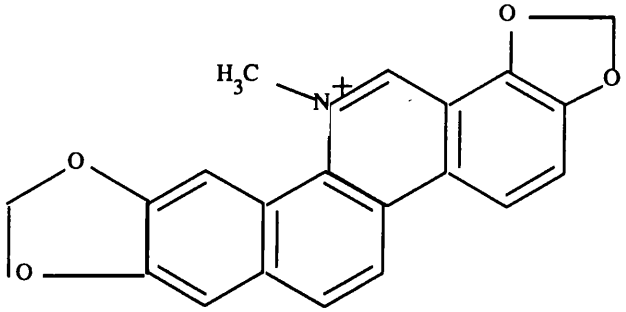
Benzophenanthridine alkaloids (BA) are isoquinoline alkaloids found particularly in species of Papaveraceae and Rutaceae. The toxicity of BA has been summarised by Simanek (1985). Cytotoxic activity *in vitro* and anti-tumour activity *in vivo* have been documented for chelidonine. Chelerythrine and sanguinarine (Figure 4.1) reportedly exhibit high anti-inflammatory activity with a low toxicity, and have been recommended for use in the treatment of oral inflammatory processes. The acute and chronic toxicity of chelerythrine in mice is reported to be low (Newall et al, 1996).

Nitidine has been investigated as an antitumour agent, although preclinical pharmacologic and toxicologic evaluations halted further research. Antitumour activity *in vivo* has been documented for fagaronine, which was stated to exhibit lower toxicity but also a narrower spectrum of activity compared to nitidine.

Figure 4.1 Chelerythrine and Sanguinarine



CHELERYTHRINE



SANGUINARINE

4.2.1.2 Bloodroot (*Sanguinaria canadensis*)

Over the last 10 years, considerable interest has been generated over the use of bloodroot extracts in oral hygiene which has prompted research into both sanguinarine and sanguinaria extracts. Initial concerns over the carcinogenic potential of sanguinarine have been disproved. Contamination of cooking oil with *Argemone mexicana* seed oil was proposed as the causative factor for endemic dropsy and associated glaucoma, with sanguinarine considered the toxic component of the seed oil (Newall et al, 1996). Subsequent workers disputed this theory and the toxicity of *A.mexicana* seed oil has been attributed to a fatty acid constituent (Newall et al, 1996). Sanguinarine has been shown to be poorly absorbed from the gastrointestinal tract, reflected by stated oral LD_{50} values (rat) of 1.7g/kg compared with an acute intravenous

LD_{50} value of 28.7mg/kg (Newall et al, 1996). Sanguinarine and sanguinaria extracts are considered suitable for use in products such as oral rinses and toothpastes.

4.2.1.3 Prickly Ash Northern/Southern (*Zanthoxylum americanum/ clava-herculis*)

Prickly ash has traditionally been used for peripheral vascular disorders and in rheumatic conditions. The main BA constituents in the Northern and Southern species are nitidine and chelerythrine, respectively.

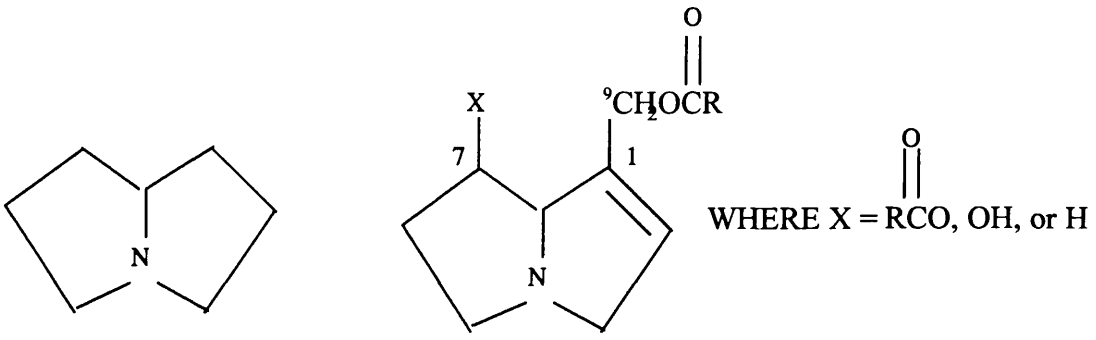
4.2.2 Pyrrolizidine Alkaloids

4.2.2.1 Chemistry and Occurrence

Pyrrolizidine alkaloids (PAs) occur globally and are present in many plant families, notably in Boraginaceae, Asteraceae (Compositae) and Leguminosae. The 1988 World Health Organisation (WHO) report on PAs (Anon, 1988b) presents a comprehensive listing of plants known to contain PAs.

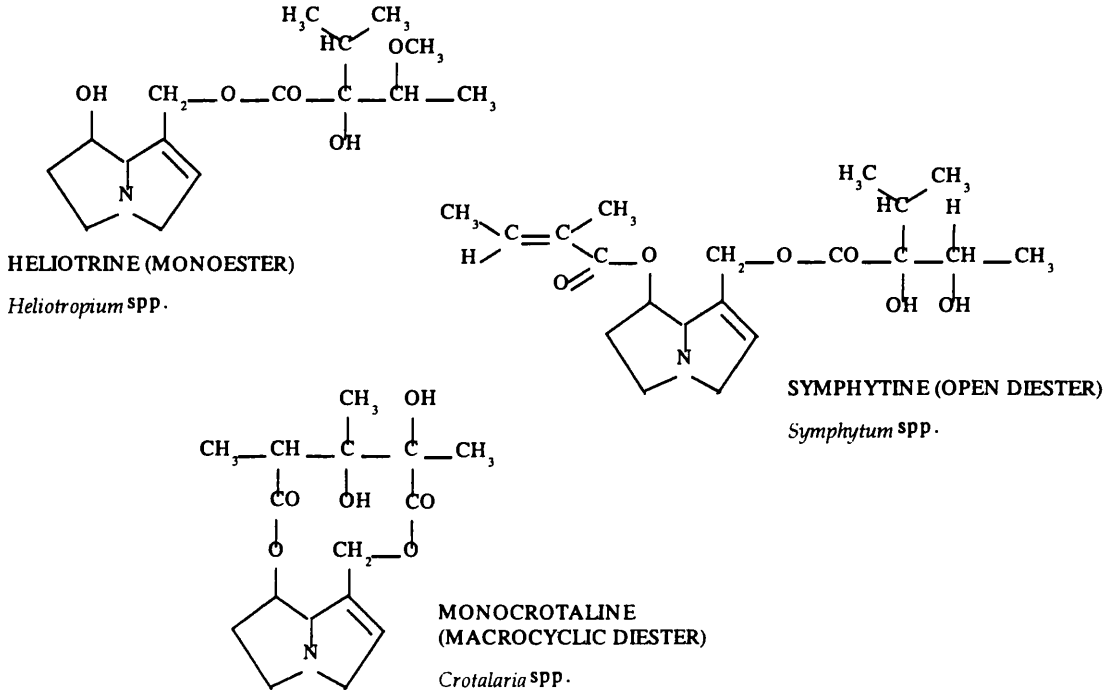
All PAs contain the basic pyrrolizidine nucleus (Figure 4.2a). PAs are esters of hydroxylated 1-methyl pyrrolizidines, and toxicity requires a 1,2-unsaturated nucleus (Figure 4.2b). The non-esterified nucleus is referred to as the necine moiety, and the esterifying acid as a necic acid (Mattocks, 1986). PAs exist as either macrocyclic diesters, open diesters or as monoesters. Some common PAs which serve as examples of these different structural types are shown in Figure 4.3

Figure 4.2 Pyrrolizidine Nucleus and Ester Structures



4.2a 4.2b

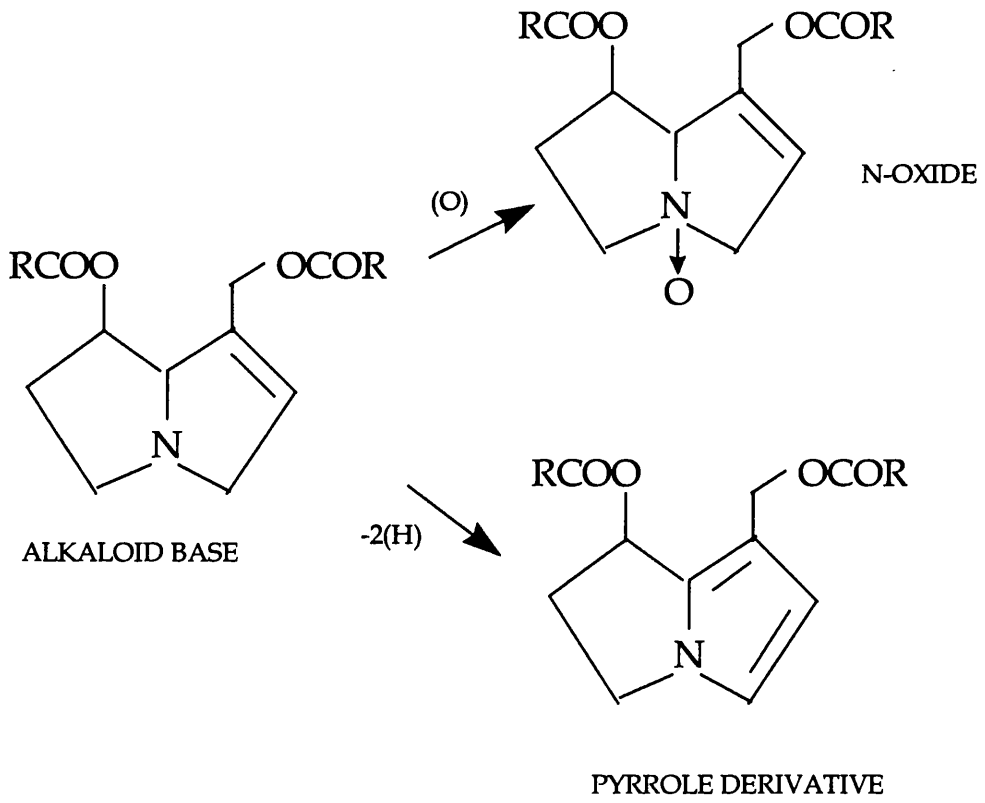
Figure 4.3 Common Pyrrolizidine Alkaloids



4.2.2.2 Formation of Pyrrole Derivatives

PA toxicity requires metabolism of the unsaturated PA nucleus into a reactive dihydroderivative, a pyrrole (Figure 4.4). In order to undergo this metabolism the PA must be unsaturated at position 1,2 with esterification of the primary hydroxyl group (Jadhav, 1982). In addition, the necic acid moiety requires a branched alkyl chain which provides steric hinderance against esterase attack of both the parent PA and the pyrrolic metabolite, and to some extent against direct hydrolysis of the pyrrole (Culvenor et al, 1985; Jadhav et al, 1982).

Figure 4.4 Pyrrole Formation



Two major types of PA metabolites are formed by hepatic metabolism: N-oxides and pyrrole derivatives (Mattocks, 1986). N-oxide formation (Figure 4.4) is a detoxication process, resulting in urinary excretion. Conversion of the N-oxides to pyrrole derivatives first requires a reduction to the parent alkaloid by intestinal flora (Mattocks,

1986). N-oxides are therefore potentially toxic if ingested. It has been suggested that PA toxicity is reflected by their rate of pyrrole formation (Anon, 1988b). *In-vitro*, the rate of pyrrole formation has been reported as highest for macrocyclic diesters, followed by open diesters and then monoesters (Culvenor et al, 1985). In addition, a macrocyclic structure is considered most resistant to esterase attack, a detoxication process (Culvenor et al, 1985). LD_{50} values (intraperitoneal) for various PAs are listed in Table 4.2. The need for oral administration to facilitate N-oxide toxicity is reflected in the values listed for lasiocarpine and retrorsine, and for their respective N-oxides.

Table 4.2 LD_{50} Values[1,2] For Hepatotoxic Pyrrolizidine Alkaloids

Alkaloid	Ester Type	LD_{50} (mg/kg)	Source
Heliotrine	Monoester	296	*Heliotropium* species
Lasiocarpine	Open diester	77	*Heliotropium* species *Symphytum* species
Lasiocarpine N-oxide	Open diester	547	*Symphytum* species
Monocrotaline	Macrocyclic diester	175	*Crotalaria* species
Retrorsine	Macrocyclic diester	34	*Senecio* species
Retrorsine N-oxide	Macrocyclic diester	250	*Senecio* species
Senecionine	Macrocyclic diester	50	Various- mainly *Senecio* species, *Tussilago farfara*
Seneciphylline	Macrocyclic diester	77	Various- mainly *Senecio* species

Alkaloid	Ester Type	LD_{50} (mg/kg)	Source
Senkirkine	Open diester	220	*Petasites* species *Senecio* species *Tussilago* species
Symphytine	Open diester	130	*Symphytum* species

[1] Rat, intraperitoneal injection
[2] Adapted from Anon, 1988b

Both saturated and unsaturated PAs are metabolised to pyrrole derivatives by hepatic microsomal enzymes, although only an unsaturated necine moiety results in the formation of a toxic metabolite (Mattocks, 1986). The toxic pyrrole metabolites of unsaturated PAs are highly reactive alkylating agents which react immediately with cell constituents, in particular proteins, to give soluble or bound secondary metabolites, or which hydrolyse to the dehydroaminoalcohol (Anon, 1976). Alkylating groups can be produced at the sites of both ester linkages in diesters, producing bifunctional alkylating agents capable of cross-linking cellular deoxyribonucleic acid (DNA) strands (McLean, 1970).

4.2.2.3 Hepatotoxicity of Pyrrolizidine Alkaloids

Three categories of hepatotoxicity have been observed in animal studies namely hyperacute (peracute), acute and chronic (Mattocks, 1986; McLean, 1970). Hepatotoxicity is clearly dose-dependent, such that sufficiently large doses of PA will cause death within a few minutes to hours of administration. The symptoms of hyperacute toxicity are related to the pharmacological actions of PAs rather than to their hepatotoxicity, and often involve convulsions (Mattocks, 1986; McLean, 1970). Acute toxicity involves necrotic lesions of the liver and death occurs within three days of PA intake. Chronic toxicity results from the administration of small, repeated doses of PAs and is characterised by the presence of greatly enlarged liver cells (hepatocytes/megalocytes) (McLean, 1970). Megalocytosis is thought to result partly

from the persistant antimitotic action of some pyrrolic esters and pyrrolic alcohols. Other features of chronic toxicity which may be present are bile duct proliferation, fatty changes, fibrosis, cirrhosis and vascular lesions (McLean, 1970).

In grazing animals, the observed toxic effects mainly fall into the acute category. PA poisoning in various animals (sheep, cattle, horses, pigs) has been associated with a number of plants including species of *Crotalaria*, *Echium*, *Heliotropium* and *Senecio* (Mattocks, 1986; McLean, 1970). In general, young animals are thought to be more susceptible to PA hepatotoxicity. Placental transfer of PAs resulting in chronic liver damage in the foetus has been documented in rats and cattle (McLean, 1970). Suckling rats have been poisoned with milk from their mothers fed PAs, who themselves remained unaffected (Mattocks, 1986).

Veno-Occlusive Disease (VOD) is the name given to the form of PA hepatotoxicity observed in humans. Clinically, VOD consists of three overlapping stages - acute, sub-acute and chronic (Stuart and Bras, 1957). Acute hepatotoxicity results from haemorrhagic necrosis of the centrilobular cells which possess enzymes capable of converting PAs to the toxic pyrroles (McLean, 1970). The lesion so formed blocks the outflow of blood from the liver. Chronic VOD may often present a histological picture indistinguishable from cirrhosis of a different aetiology and therefore cirrhosis due to VOD is rarely diagnosed. The exception is in Jamaica where widespread use of bush teas has resulted in endemic PA hepatotoxicity, and where VOD is recognised as the major cause of cirrhosis.

Chronic PA poisoning, characterised by "giant" liver cells known as hepatocytes or megalocytes, has not been reported in man (Mattocks, 1986; McLean, 1970). This is probably because man is not habitually exposed to chronic low levels of PA required for chronic toxicity. In addition, the diagnosis of liver failure in a middle-aged individual may be more readily attributed to factors such as alcohol and lifestyle rather than to long term use of a herbal remedy.

4.2.2.4 Carcinogenicity and Genotoxicity of Pyrrolizidine Alkaloids

Both individual PAs and plants containing them have exhibited weak carcinogenic activities in animals (Mattocks, 1986). Toxicity is seen mainly in the liver, regardless of the route of administration, indicating that proximate carcinogens are formed here (Mattocks, 1986). PAs that have exhibited carcinogenic activity are all esters of unsaturated necine moieties and are therefore capable of metabolism into reactive pyrroles (Mattocks, 1986). Genotoxic carcinogens interact with and alter DNA (Anon, 1996v). PAs are classified as genotoxic procarcinogens because they require conversion via host metabolic activation into primary genotoxic carcinogens, the pyrrole derivatives (Anon, 1996v). Studies with rats have reported that continuous low dose administration of PAs produces small livers with abundant megalocytes, whereas interrupted dosing produces enalarged livers with areas of megalocytes interspersed with nodules of regenerating parenchyma (McLean, 1970). This observation has been attributed to the antimitotic action of PAs, thought to prevent cell regeneration during continuous dosing (McLean, 1970). Some confusion exists over whether chronic PA poisoning results in true tumours (hepatoma) or hyperplastic growths, due to the difficulty in their distinction. A hyperplastic nodule involves an abnormal multiplication of normal cells, whereas a hepatoma represents a transition stage between an adenoma (benign) and a carcinoma (malignant) (McLean, 1970).

Antimitotic, mutagenic and other chromosone damaging effects have been documented for PAs (Culvenor, 1985; Mattocks, 1986; Petry, 1986). PAs require metabolic activation to exert maximum mutagenic activity, supporting the role of pyrrole derivatives as the proximate toxins. The carcinogenic and mutagenic activities of PAs are considered closely correlated, since it is thought that altering the genetic expression of a cell renders it in a permanent neoplastic state (Anon, 1996v).

4.2.2.5 Pyrrolizidine Alkaloid Poisoning in Humans

Crop Contamination Some of the earliest documented cases of human PA poisoning involved crop contamination, and occurred in South Africa (1920) and the USSR

(1939) where wheatfields and subsequently wheatflour were contaminated with *Senecio* and *Heliotropium* species, respectively (Anon, 1988b). The flour was made into bread and therefore gave rise to the phrase "bread poisoning". More recently epidemics of PA poisoning in Afghanistan (Mohabbat et al, 1976) and India (Tandon et al, 1976) have been documented, involving *Heliotropium* and *Crotalaria* species respectively. Additional instances of human PA poisoning from wheatflour contamination with *Crotalaria*, *Heliotropium* or *Senecio* species are listed by the WHO report (Anon, 1988b).

Food Source PA-containing plants are traditionally used as foods in a number of countries, although Mattocks (1986) reported no cases of poisoning from this source. Many species of *Senecio* are used as a form of "spinach" in South Africa, various *Crotalaria* species are used as a vegetable in East Africa, India, Indonesia and North America, and *Petasites japonicus*, a type of coltsfoot, is cultivated in Japan for use as a vegetable (Hirono et al, 1979; Mattocks, 1986). Low concentrations of PAs are also able to enter the food chain via both milk produced from cows grazing on PA-containing plants, and honey produced by bees feeding on nectar of PA-containing plants (Ridker et al, 1985). However, no reports of PA poisoning from this source appear to have been documented.

Herbal Medicines Table 4.3 lists examples of PA poisoning resulting from the use of herbal remedies. In many developing countries traditional medicines represent an important aspect of local healthcare systems. Many plants are used in the form of a tea, known as "bush teas". Not all of the plants utilised in bush teas are toxic but a number of PA-containing plants, in particular *Senecio* and *Crotalaria* species, are known to be used. Consequently, PA-poisoning has been reported in many developing countries, especially in the West Indies where bush teas are widely used (Anon, 1988b). Poisoning has been observed in both adults and children, and a number of case histories have been discussed by McLean (1970) and Stuart and Bras (1957).

Table 4.3 Examples of Pyrrolizidine Alkaloid Acute Hepatotoxicity in Man, Associated with Herbal Remedy Ingestion

Plant/Country	Patient Details	Outcome	Reference
Crotalaria / Barbados	Three children, 2-4 years	Not stated	Stuart & Bras, 1957
Crotalaria / Ecuador	Female, 35 years	Recovered	Lyford et al, 1976
Heliotropium / Hong Kong	4 Females, 23-28 years	1 Fatal, 3 recovered	Kumana et al, 1983 & 1985; Culvenor et al, 1986
Heliotropium / India	3 Adults, 20-70 years	2 Fatal	Datta et al, 1978a&b
Senecio / US	Male, 2 months	Fatal	Fox et al, 1978
Senecio / US	Female, 6 months	Recovered, cirrhosis	Stillman et al, 1977; Huxtable, 1980
Unknown / India	2 Adults, 25 & 35 years	Recovered	Gupta et al, 1963
Unknown / South Africa	12 babies	3 Fatal	Stein & Isaacson, 1962
Unknown (contaminated mate tea) / UK	Female, 26 years	Fatal	McGee et al, 1976
Symphytum / UK	Male, 13 years	Recovered	Weston et al, 1987
Symphytym / US	Female, 49 years	Recovered	Ridker et al, 1985; Huxtable et al, 1986
Tussilago & Senecio/	Female, pregnant	Fatal in baby; mother	Roulet et al, 1988

Plant/Country	Patient Details	Outcome	Reference
Switzerland		unaffected	

Instances of PA poisoning involving *Heliotropium* species have been reported in India (Datta et al, 1978a). Two patients who died were epileptic and had been taking phenobarbitone and phenytoin sodium prior to the herbal medicine (Datta et al, 1978b). Phenobarbitone potentiates the hepatic microsomal enzyme system and therefore may increase susceptibility to PA poisoning via an increase in the rate of toxic pyrrole formation.

The liver is the key organ in man affected by PA toxicity (see Table 4.4). However, the lung can also be affected and an instance of fatal primary pulmonary hypertension in an African youth has been reported for a *Crotalaria* species (Heath et al, 1975). Pneumotoxicity is characteristic for the *Crotalaria* genus.

Table 4.4 Pyrrolizidine Alkaloid Toxicity in Various Animal Species[1]

Species	Liver	Lung	Kidney	Heart	Pancreas	Gastric Mucosa	Muscle
Cattle	+	+					
Chicken	+	+	+			+	+
Dog	+						
Goat	+	+					
Horse	+	+	+				
Man	+						
Monkey	+	+	+	+			
Mouse	+		+				
Pig	+	+	+		+	+	
Rat	+	+		+		+	

Species	Liver	Lung	Kidney	Heart	Pancreas	Gastric Mucosa	Muscle
Sheep	+	+	+				
Turkey	+	+					+

[1] Adapted from Anon, 1988b

PA poisoning has also been observed in a number of industrialised countries including the United States (US), United Kingdom (UK), Hong Kong and Switzerland (Anon, 1988b). An increasing trend towards the use of alternative health systems coupled with the continuing use of native medicines by immigrants will undoubtedly result in an increasing number of observed cases of poisoning. In the UK a 13 year old boy with Crohn's disease who was receiving prednisolone and sulphasalazine therapy, was changed to treatment with comfrey and acupuncture at the request of his parents (Weston et al, 1987). The child developed VOD, recovered following hospitalisation, and orthodox treatment was resumed.

The impact of quality on the safety of herbal medicines is highlighted by the following examples:

Two reported cases of PA poisoning in Mexican-American children involved a herbal tea known as "gordolobo" (Fox et al, 1978; Huxtable, 1980; Stillman et al, 1977). "Gordolobo yerba" is the common name under which three different plants are sold, namely *Senecio longilobus*, *Gnaphalium macounii* and *Verbascum thapsus*. Only the former contains PAs (Huxtable, 1980). *S.longilobus* may well have been included in the teas by mistake, resulting from a confusion over common names. The two cases involved children of two and six months who had been given the tea to treat cold symptoms. Moreover, one of the herbal teas had been purchased from a local pharmacy where it was marketed as a sore-throat remedy (Fox et al, 1978).

In the UK, a 26 year old woman died after consuming an unknown quantity of mate (*Ilex* species) herbal tea (McGee et al, 1976), often taken as a stimulant due to the

caffeine content. Mate is not known to contain PAs, although their presence in the tea was identified following analysis. The tea may have been contaminated with a PA source, although it was possible that the woman had been exposed to another PA source (Mattocks, 1986).

PA-intoxication was reported in a 49 year old woman who had been taking a ginseng herbal tea and comfrey-pepsin pills over a 6-month period (Ridker et al, 1985). Surprisingly, both the pills and the tea were found to contain toxic PAs in both their free base and N-oxide states. Ginseng is not known to contain any PAs.

Fatal paediatric hepatotoxicity resulting from maternal consumption of a herbal tea throughout pregnancy has been reported in Switzerland (Roulet et al, 1988). The tea was purchased from a local pharmacy as an expectorant and contained 10 different plants including coltsfoot. Coltsfoot is only known to contain non-toxic PAs, although the presence of a *Senecio* species was also suggested. The susceptibility of children to PA toxicity was highlighted by a lack of hepatotoxicity in the mother.

Four chinese women presented with PA poisoning in Hong Kong, following their consumption of a herbal tea for psoriasis imported from India (Kumana et al, 1985). One of the women died and a subsequent analysis of the tea revealed *Heliotropium lasiocarpum* as a constituent (Culvenor et al, 1986).

4.2.2.6 Comfrey (*Symphytum officinale*)

Comfrey root and leaf are commonly used as a herbal remedy for the treatment of ulcers and arthritis (internally) and of wounds (externally). Comfrey belongs to the same plant family as *Heliotropium* species (Boraginaceae) and has been reported to contain a number of hepatotoxic alkaloids including symphytine, heliosupine, echimidine and lasiocarpine (Newall et al, 1996). Comfrey (Hirono et al, 1978) has exhibited carcinogenic properties in rats. Mutagenic activity has been documented for comfrey root extracts in meristematic cells of *Vicia faba* L. var *minor* (Furmanowa et al 1983), although leaf extracts were reportedly devoid of activity when tested in

Salmonella typhimurium, mice, and mouse hepatic microsomes (Lim-Sylianco et al, 1977). Mutagenic activity has been reported for both lasiocarpine and echimidine (Furuya et al, 1987) Human hepatotoxicity has been documented for comfrey (see Table 4.3) and Section 4.2.1.6.

In view of the hepatotoxic potential of comfrey, it is not permitted to be included in medicines intended for internal use. Comfrey may be included in a licensed product intended for topical use, providing application is to unbroken skin and that use is restricted to ten days or less at any one time (Newall et al, 1996). Comfrey has traditionally been used in food supplements and in herbal teas. Following a report by the Committee on Toxicity of Chemicals in Food to the Ministry of Agriculture, Fisheries and Food, the health food trade voluntarily withdrew all products, such as tablets and capsules, containing comfrey. Advice was also issued that comfrey roots and leaves should be labelled with warnings against ingestion. Comfrey teas were considered to contain relatively low levels of pyrrolizidine alkaloids and did not therefore warrant any warning labels (Newall et al, 1996). However, a cup of comfrey root tea made according to the directions on the package was estimated to contain between 8.5-26mg total PA (free base and N-oxide) per cup (Roitman, 1981), a potentially toxic dose when compared to the PA doses associated with human cases of VOD (see Table 4.5).

Table 4.5 Pyrrolizidine Alkaloid Doses In Documented Cases of Acute Veno-Occlusive Disease

Plant / Patient	Total PA Dose (mg)/ Duration[1]	Outcome	Reference
Heliotropium lasiocarpum			
Female, 28 years	1350mg (26mg/kg) / 45d	Recovered	Kumana et al, 1983 & 1985;
Female, 26 years	1403 mg (23mg/kg) / 30d	Fatal	Culvenor et al, 1986

Plant / Patient	Total PA Dose (mg)/ Duration[1]	Outcome	Reference
Female, 27 years	630mg (15mg/kg) / 21 d	Asymptomatic	
Female, 23 years	570mg (12mg/kg) / 19d	Recovered	
Senecio longilobus			
Child, 2 months	66mg (13mg/kg) / 4d	Fatal	Fox et al, 1978
Child, 6 months	70-147mg (9-18mg/kg) / 14d	Recovered	Stillman et al, 1977; Huxtable, 1980
Symphytum officinale			
Female, 49 years	85mg (15ug/kg[2]) / 6 months	Recovered	Ridker et al, 1985; Huxtable et al, 1986

[1] d = days
[2] Daily Dose

4.2.2.7 Coltsfoot (*Tussilago farfara*)

Coltsfoot leaf is commonly used in herbal preparations as an expectorant and antitussive, attributable to the mucilage content which has a demulcent action. Coltsfoot belongs to the Asteraceae (Compositae) plant family which contains a number of PA-containing genera including *Senecio*. Coltsfoot contains low levels of PAs, the main constituent being an unsaturated alkaloid senkirkine (0.015%) (Culvenor et al, 1976). The low level of PAs in coltsfoot is not considered to represent a health hazard and coltsfoot is permitted in herbal medicines intended for internal use. The risk of longterm exposure to low levels of PAs is unclear, although the potential risk was highlighted by a study in which chronic exposure (600 days) of rats to coltsfoot (at 4%

or greater in diet) resulted in hepatotoxicity (tumours or necrosis) (Hirono et al, 1979). Prolonged consumption of coltsfoot is therefore not advisable. Both carcinogenic and mutagenic activity have been reported for the PA constituents in coltsfoot (Anon, 1988b). Fatal hepatic VOD has been documented in a newborn infant whose mother had regularly consumed a herbal tea during pregnancy (Roulet et al, 1988). Analysis of the herbal tea revealed the presence of 10 different plants including coltsfoot and a *Senecio* species.

4.2.2.8 Borage *(Borago officinalis)*

Borage herb has been traditionally used to treat a variety of ailments including fevers, coughs and depression (Newall et al, 1996). In recent years borage oil (also referred to as starflower oil) has received considerable interest as a source of γ-linolenic acid, representing an alternative to evening primrose oil and blackcurrant oil. Borage belongs to the same plant family as comfrey (Boraginaceae) and has been reported to contain a number of unsaturated PAs including lycopsamine, amabiline, supinine and intermidine, albeit at low concentrations (Newall et al, 1996).

4.2.2.9 Echinacea (*Echinacea officinalis*)

Traditionally, echinacea has been used for its reputed antiseptic and antiviral properties. More recently, it has been investigated for a potential immunostimulant action. Only saturated PAs (i.e. non-toxic) have been documented for echinacea and at very low levels. The PA content of echinacea is therefore not considered to represent a health risk.

4.2.2.10 Liferoot *(Senecio aureus)*

Traditionally, liferoot has been used for its reputed diuretic and expectorant properties. The *Senecio* genus is well known for its unsaturated pyrrolizidine alkaloid constituents. In view of this, liferoot is not permitted for use in licensed herbal products.

4.2.2.11 Health Risk of Human Exposure to Pyrrolizidine Alkaloids

The acute effects of PA poisoning in humans have been described in detail as hepatic veno-occlusive disease (VOD) (McLean, 1970; Stuart & Bras, 1957). The possible risks of chronic exposure to low levels of PAs is unclear. The longterm effects of acute exposure to PAs are known to be hepatic cirrhosis. It has been stated that cirrhosis is an important precursor of liver malignancy, since both are associated with active hepatic regeneration following cell destruction (McLean, 1970). Results of epidemiological studies, however, have not always supported this theory (McLean, 1970). Table 4.5 lists some examples of PA doses ingested in cases of poisoning. The first four cases involving *Heliotropium lasiocarpum* highlight the individual variation in susceptibility to PA poisoning. On a mg/kg bodyweight basis, the second woman listed died despite ingesting less than the first woman, who recovered. The low doses of *Senecio longilobus* ingested by two infants highlight the increased susceptibility of children to PA poisoning. The potential danger of chronic, low level PA exposure is highlighted by the case associated with *Symphytum officinale*, in which the woman ingested only 15mcg/kg bodyweight over a 6 month period.

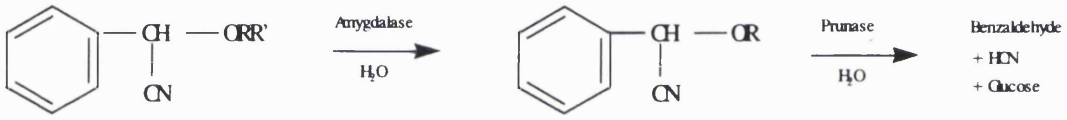
4.2.3 Cyanogenetic Glycosides

4.2.3.1 Chemistry, Occurrence, Toxicity

Cyanogenetic glycosides occur in many plants, with over 2000 plant species involving about 110 families estimated to be cyanogenetic (Evans, 1996). Many of the glycosides are derived from the nitrile of mandelic acid. The sugar portion of the molecule may be a monosaccharide or a disaccharide such as gentiobiose or vicianose. The toxicological significance of these compounds follows their hydrolysis, which results in the liberation of hydrogen cyanide (HCN). Figure 4.5 shows the two step hydrolysis of the cyanogenetic glycoside amygdalin resulting in the liberation of HCN. Hydrolysis can be carried out by β-glucosidases, heat, mineral acids or high doses of vitamin C. In

humans, cyanogenetic glycosides present a potential health risk when consumed in large quantities resulting in abnormally high HCN levels. The usual physiological methods of dealing with cyanide ingestion, namely exhalation or rapid conversion to the less toxic thiocyanate by the enzyme rhodanese, become saturated and cyanide poisoning results. Cyanogenetic glycoside-containing plants are not commonly utilised in EC herbal remedies. However, this section is referred to in this chapter because of a significant health hazard presented by a semi-synthetic substance known as laetrile in the late 1970's and early 1980's (Newall et al, 1996).

Figure 4.5 Liberation of Hydrogen Cyanide from Amygdalin



Amygdalin
(ORR' = gentiobiose)

Prunasin
(OR = glucose)

4.2.3.2 Laetrile/Apricot

Laetrile is a semi-synthetic derivative of amygdalin. Natural sources of amygdalin include the apricot kernel. In the late 1970's and early 1980's considerable interest was generated in apricot from claims that laetrile was an effective treatment for cancer (Newall et al, 1996). The three proposed theories for the action of laetrile were either disproved or considered untenable (Chandler et al, 1984a & 1984b) However, apricot kernels were seen as an alternative source of this miracle cure and consumed in toxic quantities.

Laetrile and apricot kernel ingestion are the most common sources of cyanide poisoning, with more than 20 deaths reported (Chandler et al, 1984a & 1984b). β-glucosidases, enzymes that hydrolyse amygdalin to release HCN, are not normally

abundant in the gastro-intestinal tract. However, they are present in the kernels themselves and in certain foods including beansprouts, carrots, celery, green peppers, lettuce, mushrooms and sweet almonds. Hydrolysis of the amygdalin molecule is slow in an acid environment but much more rapid at an alkaline pH. There may therefore be a delay in the onset of cyanide poisoning symptoms reflecting the transit time from the acid pH of the stomach to the alkaline environment of the small intestine.

Oral doses of 50mg HCN can be fatal. This is equivalent to approximately 30g kernels which represents about 50-60 kernels at approximately 2mg HCN/g kernel (Newall et al, 1996). However, apricot kernels have been reported to contain 2.92mg HCN/g kernel. In addition, a 500mg laetrile tablet was reported to contain between 5 and 51mg HCN/g (Holzbecher et al, 1984). There may be considerable variation in the number of apricot kernels required to be toxic, depending on the concentration of amygdalin and β-glucosidases present in the kernels, the time span of ingestion, concomitant foods ingested, the degree of maceration of the kernel, and individual variation in hydrolysing and detoxifying abilities (Newall et al, 1996).

In order to reduce the potential risk to the general public, the following herbal remedies were made prescription-only medicines in 1984: preparations labelled as amygdalin, laetrile, or vitamin B_{17}, or preparations with a cyanogenetic glycoside content exceeding 0.1%w/w (Anon, 1984c).

4.2.4 Diterpenes

4.2.4.1 Chemistry, Occurrence, Toxicity

Diterpenes comprise four isoprene (C_5) units and are represented by constituents such as resin acids, phytol, and vitamin A (Sticher, 1977). Diterpenes are widely distributed compounds occurring in plants, fungi and animals and present a diverse range of structural types. In addition to a number of pharmacological activities such as antibiotic, antitumour, insecticidal and purgative, toxic activities such as severe irritant,

cocarcinogenic and cytotoxic are also documented. One particularly well investigated group of diterpenes are known as phorbol, ingenane or daphnane esters depending on their structural type. These three related structure types occur in the Euphorbiaceae (e.g. *Euphorbia* spp. and *Croton tiglium*) and the Thymelaceae (e.g. *Daphne*, *Lasiosiphon*, *Pimelia*, and *Gnidia* spp.) Severe irritant and cocarcinogenic activities are well documented for these compounds. Few EC plants used as herbal remedies contain these toxic constituents, although Queen's Delight is an example.

4.2.4.2 Queen's Delight (*Stillingia sylvatica*)

Queen's Delight (*Stillingia sylvatica*) root has traditionally been used for inflammatory conditions of the throat and lungs, for skin conditions, haemorrhoids and constipation (Newall et al, 1996). In view of the potentially irritant and toxic properties of the diterpene ester constituents in Queen's Delight, its use in licensed medicines is restricted to a maximum dose of 320mg (Anon, 1984b).

4.2.4.3 Germander (*Teucrium chamaedrys*)

Reports of hepatotoxicity, one fatal, have been associated with the ingestion of wild germander (*Teucrium chamaedrys*), a herb used in Europe (but not commonly in the UK) for obesity (Larrey et al, 1992; Mostefa-Kara et al,1992). In the seven patients reported by Larrey et al, no other cause of hepatitis was found. The time to onset of hepatitis was, on average, 9 weeks with a positive dechallenge observed in all seven patients (hepatitis resolved following germander discontinuation), and a positive re-challenge observed in the three patients to whom germander was re-administered (Larrey et al, 1992). The liver injury induced by germander was non-specific and a mechanism of action could not be determined. Loeper et al (1993) studied the mechanism of germander hepatotoxicity in mice, and concluded that toxicity is mediated by toxic furanoditerpenoid metabolites formed by cytochrome $P\text{-}_{450}$. In April 1992, the sale of wild germander was prohibited by the French Department of Health, following 26 reports of hepatitis associated with its ingestion (Mostefa-Kara et al, 1992).

There have been a number of documented cases of hepatitis associated with multi-ingredient herbal preparations all containing scullcap, and with no obvious hepatotoxic herbal ingredient (Harvey & Colin-Jones,1981; MacGregor et al,1989). However, it is now well recognised that commercial scullcap is adulterated with a *Teucrium* species, notably *Teucrium canadense*, known to also contain diterpenoid constituents (see Chapter 3, Section 3.3.1).

4.2.5 Essential Oils

An essential oil is a fragrant, volatile liquid extracted by distillation (or cold expression for citrus oils) from a single botanical source. Essential-oil producing plants are widely distributed, and most essential oils contain at least 100 components, with about two or three major components (Tisserand & Balacs, 1995). Terpenes, terpenoids and alkenylbenzene derivatives constitute the chief components of volatile oils, and a few of these compounds from the latter two types are associated with a marked toxicity. Other less common components such as acids, oxides, lactones, sulphur compounds and nitrogen compounds may represent the toxic constituents. Furanocoumarin compounds (lactones), which are also present in essential oils, are discussed under Section 4.2.6.

Of the many essential oil components, only a small number are hazardous. Some of the principle toxic essential oil components of herbs used in EC herbal remedies are listed in Table 4.6, and are discussed below under alkenylbenzene derivatives and terpenoids.

Table 4.6 Toxic Constituents of Essential Oils[1]

Constituent	Toxic Effect	Example of Herb (% in oil)
Alantolactone	Skin sensitiser	Elecampane (52%)
Apiole[2]	Irritant, abortifacient	Parsley seed (21-80%) Parsley leaf (<18%)
β-Asarone[2]	Convulsive, carcinogenic, genotoxic, hepatotoxic	Calamus (0-96%)
Ascaridole	Convulsive, irritant	Boldo leaf (16%) Wormseed (60-80%)
Camphor	Convulsive, toxic	Rosemary (10-20%) Sage-Dalmatian (1-26%) Sage-Spanish (11-35%) Yarrow (10-20%)
Carvacrol	Irritant	Oregano (0.5-84%) Savory (3-67%) Thyme (1-44%)
Cinnamic aldehyde	Skin sensitiser	Cassia (75-90%) Cinnamon bark (60-75%)
Estragole[2]	Carcinogenic, genotoxic	Basil (5-87%) Fennel (2-7%) Tarragon-French (70-87%)
Eugenol	Irritant	Clove leaf (70-90%)
Isothiocyanates	Irritant	Horseradish (95%) Mustard (99%)

Constituent	Toxic Effect	Example of Herb (% in oil)
Myristicin[2]	Psychoactive	Mace (1.5-3.8%) Nutmeg (2-10%) Parsley leaf (7-33%) Parsley seed (28%)
Pinocamphone	Convulsive	Hyssop (40%)
Pulegone	Hepatotoxic	Buchu (50%) Pennyroyal -European (55-90%) -N. American (60-80%)
Sabinyl acetate	Abortifacient, embryotoxic, fetotoxic, teratogenic	Sage-Spanish (0.1-24%) Savin (20-53%)
Safrole[2]	Carcinogenic, genotoxic	Sassafras (85-90%)
Thujone	Convulsive, toxic	Mugwort (major) Sage-Dalmatian (50%) Tansy (66-81%) Thuja (39-80%) Wormwood (34-71%)

[1] Tisserand & Balacs, 1995 [2] Discussed under Alkenylbenzene derivatives

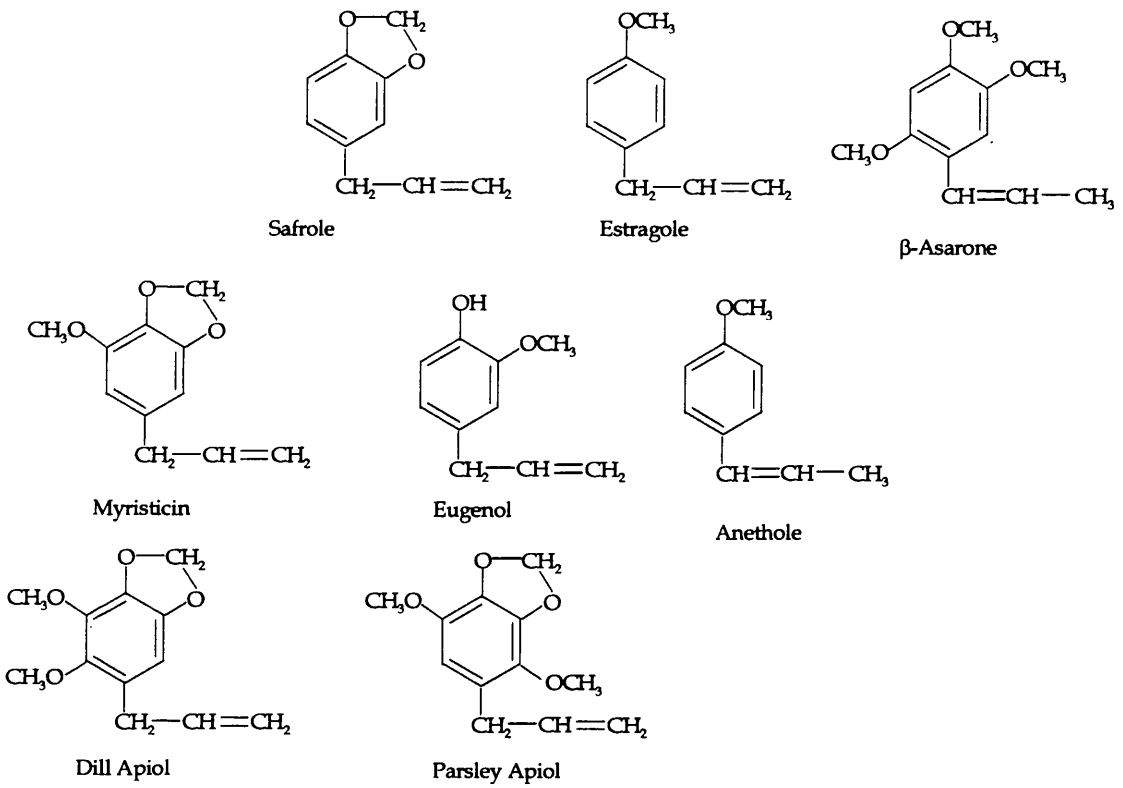
4.2.5.1 Alkenylbenzene Derivatives

Alkenylbenzene derivatives are common essential oil constituents of many herbs and spices. In the 1960's the reported carcinogenicity of one of these compounds, safrole, raised concerns over the toxicity of a number of structurally related compounds that are commonly used as food flavourings (Tisserand & Balacs, 1995). Toxicity studies have

therefore been carried out for many alkenylbenzene derivatives in order to assess their potential toxicity in humans. When extrapolated, the doses used in animal toxicity studies far exceed the doses ingested in the human diet. This high dosing will undoubtedly result in saturation of normal metabolic pathways of the compounds and possibly to the formation of different metabolites, or to an accumulation of an unmetabolised parent compound or of an intermediate metabolite (Tisserand & Balacs, 1995). Whether or not naturally occurring alkenylbenzene derivatives are important in the aetiology of human cancers is unknown. In perspective, the carcinogenic activity documented for safrole and estragole indicate them to be very weak carcinogens in comparison with pyrrolizidine alkaloids and aflatoxins (Miller & Miller, 1979).

A number of alkenylbenzene derivatives (Figure 4.6) are also constituents of herbs used medicinally in herbal remedies, and these are considered briefly below. The therapeutic dose of a herb or spice used as a herbal remedy will usually exceed the amount used in foods. This is an important consideration when considering the safety of a culinary herb used for medicinal purposes. In general, excessive or prolonged ingestion of a culinary herb in amounts that far exceed those used in foods is not recommended.

Figure 4.6 Alkenylbenzene Derivative Constituents of Medicinal Herbs



Induction of cytochrome $P\text{-}_{450}$ activity has been associated with the mutagenic and carcinogenic activity of the inducing agent (Iwasaki et al, 1986). Structure-activity studies on the induction of cytochrome $P\text{-}_{450}$ and $P\text{-}_{448}$ have reported that oxidation of the allyl sidechain increases the affinity for $P\text{-}_{448}$ and markedly decreases the induction of $P\text{-}_{450}$. The presence of a methylenedioxy group further enhances the induction of mixed function oxidases. Therefore compounds with both an intact allyl sidechain and a methylenedioxy group (e.g. safrole, myristicin) represent the most potent inducers of cytochrome $P\text{-}_{448}$ and $P\text{-}_{450}$. Compounds with an intact allyl sidechain only (e.g. estragole) represent inducers of $P\text{-}_{448}$ only (Ionnides et al, 1985). However, myristicin is reported to lack carcinogenic activity suggesting, possibly, that it is not metabolised into reactive metabolites. This has been attributed to the more complex structure of myristicin which inhibits 1'-hydroxylation of the allyl side-chain (Tisserand & Balacs, 1995), an important step in converting the parent molecule to a reactive metabolite.

It has been documented that a general correlation exists between the carcinogenic activity of a chemical and its genotoxic activity in *Salmonella typhimurium* (Swanson et al, 1979). The ultimate carcinogens of many chemicals are strong electrophiles which react with nucleophilic groups on DNA and other cellular macromolecules (To et al, 1982). However, conflicting results have been documented regarding the mutagenicity of known carcinogenic compounds such as safrole, and this has been attributed to sample purity and sample toxicity in the bacterial test strain (Sekizawa & Shibamoto, 1982), different bacterial test strains and activating systems, and different assay methods used with *Salmonella* (To et al, 1982).

4.2.5.1.1 Safrole

Safrole is the major component of sassafras oil and is obtained by steam distillation from the roots and bark of *Sassafras officinale* or *S.albidum*. Safrole was formerly used as a flavouring agent in beverages including root beer (Newall et al, 1996). Safrole was first recognised as a hepatocarcinogen in the 1960's (Homburger & Boger, 1968) and many animal toxicity studies have been documented concerning this toxicity (Opdyke, 1982). Both benign and malignant tumours have developed in laboratory animals depending on the dose of safrole administered (Opdyke, 1974b). Both human and animal studies have shown that safrole gives rise to a large number of metabolites (Ioannides et al, 1981). A sulphate ester (formed via a hydroxylated metabolite) has been established as the ultimate carcinogen for safrole with tumour incidence paralleling the rate of conversion to the ester (Bock & Schirmer, 1987). Induction of cytochrome $P\text{-}_{450}$ activity has been associated with the mutagenic and carcinogenic activity of the inducing agent (Iwasaki et al, 1986). The inducing effect of safrole on certain metabolising enzymes is thought to play a role in the carcinogenic activity of safrole. The liver has a high level of cytochrome $P\text{-}_{450}$ and is therefore susceptible to induction (Iwasaki et al, 1986). Conflicting results have been reported from studies investigating the mutagenicity of safrole, using the Ames test and DNA repair test (Sekizawa & Shibamoto, 1982; Swanson et al, 1979). Purity of the safrole, test system

employed, type of metabolic activation mix, and toxicity of the test system have been suggested as reasons for the observed variations (Sekizawa & Shibamoto, 1982).

In the US, the use of safrole as a food additive was banned in 1961. In the EC and UK, the use of safrole as a food flavouring is permitted to 1mg/kg (Tisserand & Balacs, 1995). In the UK, sassafras is not permitted as an ingredient of licensed herbal remedies.

4.2.5.1.2 Estragole (Methylchavicol)

Eastragole occurs naturally in the oils of herbs such as tarragon, bay, basil and fennel. The toxicity of estragole has been studied alongside safrole, in view of their strucural similarities. As with safrole, metabolism of the allyl side chain plays an important role in the toxicity of estragole. A sulphate ester (formed via a hydroxylated metabolite) has been established as the ultimate carcinogen for estragole with tumour incidence paralleling the rate of conversion to the ester (Bock & Schirmer, 1987). Hepatocarcinogenicity studies in mice have reported estragole as 2-3 times more potent than safrole derivatives (Wiseman et al, 1987).

4.2.5.1.3 β-Asarone

In the 1960s, feeding studies in rats reported that calamus oil (high β-asarone content) resulted in death, growth depression, hepatic and heart abnormalities, serous effusion in abdominal and/or peritoneal cavities, and malignant duodenal tumours (Taylor et al, 1967; Gross et al, 1967). Genotoxic (human lymphocytes) and mutagenic (Ames) activities have been documented for β-asarone, in the presence of a microsomal activation mix (Abel, 1987; Goggelmann & Schimmer, 1983). The requirement of microsomal activation to observe genotoxic and mutagenic activities suggests hepatic metabolism of β-asarone to a reactive electrophile. In view of the reported toxicity of β-asarone, its use as a flavouring agent is restricted to 0.1mg/kg in foods and beverages,

and to 1mg/kg in alcoholic beverages and in foods containing *A.calamus* or *Asarum europaeum*.

β-Asarone is the principle constituent of the essential oil of Calamus rhizome (*Acorus calamus*). The β-asarone content of the essential oil differs considerably between genetic species: 96% in tetraploid, 5% in triploid (European), and 0% in the diploid (North American) species (Keller & Stahl, 1983; Mazza, 1985a and b; Stahl & Keller, 1981). Calamus is reputed to have carminative, spasmolytic and diaphoretic properties and has traditionally been used to treat gastro-intestinal disorders. In view of the toxicity associated with β-asarone, it is advised that only calamus roots free from, or with a low content of β-asarone, should be used in human phytotherapy (Goggelmann & Schimmer, 1983).

4.2.5.1.4 *trans*-Anethole, Apiole, Eugenol, Myristicin

These four compounds, all common constituents in culinary herbs and structurally similar to sassafras, have not been found to demonstrate any carcinogenic activity and have no or low level genotoxic activity (Miller et al, 1983; Tisserand & Balacs, 1995). *trans*-Anethole (the *cis*-isomer is many times more toxic but rarely occurs in essential oils) exhibits weak oestrogenic activity. Anethole-rich oils should therefore be avoided in people with oestrogen-dependent cancers, and should not be taken orally by women who are pregnant, breast-feeding, or have endometriosis (Tisserand & Balacs, 1995). Apiole is toxic and abortifacient, and fatalities have been recorded following its ingestion (see Section 4.5) (Tisserand & Balacs, 1995). In common with many phenolic essential oil components, eugenol is a mucous membrane irritant. Eugenol-rich oils should not be taken orally by individuals whose blood clots slowly (anti-platelet activity) or with paracetamol, and used with caution by individuals with impaired liver function (hepatotoxicity observed in glutathione-depleted mice) (Tisserand & Balacs, 1995). Psychotropic effects are well documented for nutmeg and mace oils and are attributed to myristicin, although other myristicin-rich oils such as parsley and parsnip have not been associated with such effects(Tisserand & Balacs, 1995).

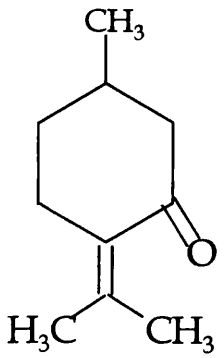
4.2.5.2 Terpenes

Essential oils contain numerous hydrocarbon (terpene) and oxygenated terpene compounds (terpenoids), based on the monoterpene (C_{10}) or, less commonly, sesquiterpene (C_{15}) unit. The toxicity of terpene constituents is mainly associated with the oxygenated compounds such as alcohols, aldehydes, ketones and phenols.

4.2.5.2.1 Pulegone

Pulegone (Figure 4.7) is a monoterpene ketone present as the major constituent of pennyroyal (*Mentha pulegium, Hedeoma pulegoides*) and buchu (*Agathosma betulina, A.crenulata*) essential oils. Traditionally, pennyroyal herb has been used for its reputed carminative, antispasmodic and emmenagogue properties, and buchu for reputed urinary antiseptic and diuretic properties (Newall et al, 1996). Pulegone is metabolised by cytochrome $P\text{-}_{450}$ to highly reactive furan metabolites which are then able to destroy the $P\text{-}_{450}$ (Tisserand & Balacs, 1995).

Figure 4.7 Pulegone



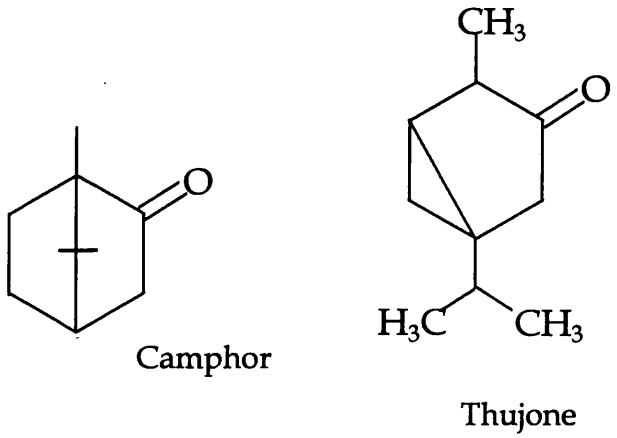
The toxicity of pennyroyal oil is well recognised and human fatalities following its ingestion as an abortifacient have been reported (Gunby, 1979; Sullivan et al, 1979; Vallance, 1955). See Section 4.5 for further details. Toxicity associated with the

ingestion of pennyroyal herb, rather than the oil, has not been documented. Indeed, it has been reported that pennyroyal herb teas have been used without any side-effects (Sullivan et al, 1979). No reports of poisoning with buchu herb or oil were located.

Both buchu and pennyroyal oils are unsuitable for either internal or external use. In the EC and UK, the use of pulegone as a food flavouring is limited to 25mg/kg (Tisserand & Balacs, 1995).

4.2.5.2.2 Camphor and Thujone

Figure 4.8 Camphor and Thujone

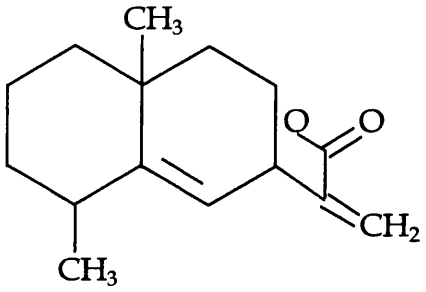


Camphor and thujone (Figure 4.8) are monoterpene ketones present as key components in the essential oils of various herbs including rosemary (camphor-only), sage, tansy (thujone-only), and yarrow. Convulsive actions have been documented for both compounds in animal toxicity studies (Tisserand & Balacs, 1995). Convulsant activity has been documented in both animals and humans for sage oil (Millet, 1980; Tisserand & Balacs, 1995). Fatalities have been reported following the ingestion of tansy oil, infusions and powders (Hardin & Arena, 1974; Opdyke, 1976). In the EC and UK, the use of thujone as a food flavouring is limited to 0.5mg/kg (Newall et al, 1996). Tansy

oil is prohibited from use as a food flavouring by the Food Additives and Contaminants Committee (Newall et al, 1996).

4.2.5.2.3 Alantolactone, Ascaridole and Sabinyl Acetate

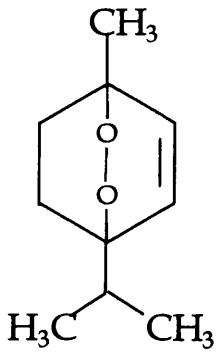
Figure 4.9 Alantolactone



Alantolactone (Figure 4.9) is a sesquiterpene lactone and is the major constituent of elecampane (*Inula helenium*) essential oil. Traditionally elecampane has been used for its reputed expectorant, antitussive, diaphoretic and bactericidal properties (Newall et al, 1996). Reports of contact dermatitis have been documented for elecampane and attributed to the sesquiterpene lactone constituents of the essential oil. For further discussion on sesquiterpene lactones see Section 4.3.2.

Ascaridole (Figure 4.10) is a terpene peroxide present in the essential oil of boldo leaf (*Peumus boldus*) , which has been used traditionally for gallstones, cystitis and rheumatism (Newall et al, 1996). Boldo oil is considered one of the most toxic essential oils, and is unsuitable for either internal or external use. The toxicity of boldo essential oil is attributable to the ascaridole content (Tisserand & Balacs, 1995).

Figure 4.10 Ascaridole



Sabinyl acetate is a toxic terpene ester present in savin and in some Spanish sage oils. Neither of these herbs are commonly used in EC herbal remedies, although savin (*Juniperus sabina*) has been confused with juniper (*Juniperus communis*) which is used in EC herbal remedies. Refer to Section 4.5 for further discussion on the toxicity of savin.

4.2.5.2.4 Sulphur Compounds

Sulphur compounds are pungent, reactive molecules that are present in only a few essential oils, and which are not terpene derived. Mustard and horseradish essential oils are particularly toxic (irritant), and this is attributed to their sulphur component allyl isothiocyanate (Tisserand & Balacs, 1995).

4.2.5.2.5 Discussion

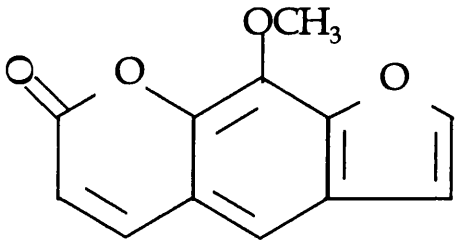
A number of essential oils contain highly toxic components and are considered unsuitable for internal and/or external use. The examples of herbal sources listed in Table 4.6 contain some herbs that are commonly used in foods and/or are ingredients of licensed herbal medicines. This may seem somewhat surprising but underlines the importance of the dose ingested of a toxic compound. There is a significant difference

between the ingestion of an undiluted essential oil and of a herb containing the essential oil. Basil, clove, fennel, nutmeg, parsley, sage and thyme are all commonly used in foods and present no health risk in view of the small quantities ingested. When considering the use of medicinal herbs containing toxic essential oils, such as boldo, buchu, elecampane and yarrow (in addition to many of the culinary herbs and spices already mentioned), it is again important to determine the intended dose of the toxic components. Many essential oil-yielding plants contain small quantities of the oil, and the amount present in the finished medicinal product may be significantly reduced by extraction and formulation processes used. Maximum permitted food levels and documented toxicological values, such as LD_{50}, can be used to assist in calculating an acceptable dose of a herbal ingredient.

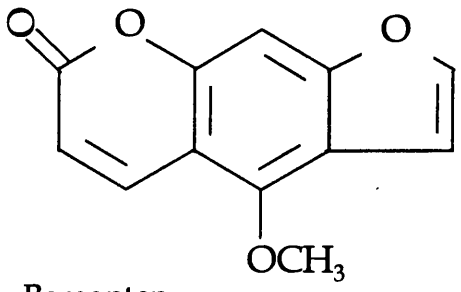
4.2.6 Furanocoumarins

Furanocoumarins (or psoralens) are derivatives of coumarins and occur particularly in the families Rutaceae and Umbelliferae. Two common furanocoumarins are bergapten and xanthotoxin (Figure 4.11). The phototoxic properties of furanocoumarins are well documented and phototoxic essential oils include angelica, bergamot, cumin, citrus oils (expressed), and rue. A phototoxic agent absorbs energy from UV light and then uses this energy to damage the skin. Phototoxic components occur in only a few essential oils and in relatively small amounts, normally less than 2%. Even when diluted, these essential oils can still produce a phototoxic reaction following exposure of the skin to sunlight (Tisserand & Balacs, 1995). For further discussion on phototoxic reactions with herbal remedies, refer to Section 4.3.3.

Figure 4.11 Bergapten and Xanthotoxin



Xanthotoxin



Bergapten

4.2.7 Lignans

4.2.7.1 Chemistry, Occurrence and Toxicity

Lignans are dimers of two phenylpropane units and are widely distributed in the plant kingdom (Ayres & Loike, 1990). Lignans have been identified in species belonging to 70 plant families and also in mammalian species, including man. Lignans possess a diverse spectrum of biological properties suggesting a variety of mechanisms of action (Ayres & Loike, 1990). Suggestions for their role in mammals include a hormonal activity, of alimentary origin, or metabolic products of gut microflora (Massanet et al, 1989) Toxicological actions associated with lignans used medicinally include cytotoxicity (podophyllum) and hepatotoxicity (chaparral).

4.2.7.2 Podophyllum (*Podophyllum pelatum*)

Podophyllum consists of the dried rhizome and roots of *Podophyllum pelatum*. The lignan constituents represent the active principles in the resin, the main components being podophyllotoxin, α- and β-peltatin. The cytotoxic properties of the resin are utilised in paints used in the treatment of warts. The use of podophyllum and

podophyllum resin are restricted to Pharmacy Only or Prescription Only Medicines (Anon, 1983b)

4.2.7.3 Chaparral (*Larrea tridentata*)

Chaparral refers to the above ground parts of *Larrea tridentata* (Newall et al, 1996). Chaparral originates in South-west US and in Northern Mexico, and does not have a traditional use as a herbal remedy within Europe. In the US, chaparral has been used for various ailments including arthritis and rheumatism, cancer, venereal disease, tuberculosis, bowel cramps, and colds (Tyler, 1993). Chaparral is included in this discussion in view of recent concerns over its risk to human health (Anon, 1992a & 1993a; Clark & Reed, 1992; Gordon et al, 1995; Katz & Saibil, 1990).

Chaparral contains a number of lignan constituents, the principle one being nordihydroguaiaretic acid (NDGA). NDGA was formerly used as an antioxidant in foods. Early investigations into the toxicity of NDGA concluded it to be low (Oliveto, 1972) However, subsequent feeding studies in rats reported the development of cortical and medullary cysts in the kidney (Oliveto, 1972). On the basis of these observations NDGA was no longer permitted to be used as an antioxidant in foods in the US. Cases of acute hepatitis and of irreversible reno-hepatic failure, associated with the ingestion of chaparral-containing products, have been reported in Canada and the US (Anon, 1992a & 1993a; Clark & Reed, 1992; Gordon et al, 1995; Katz & Saibil, 1990). In 1995, the American Herbal Products Association reportedly rescinded the voluntary withdrawal of chaparral from sale (Shaw et al, 1996).

4.2.8 Lectins and Viscotoxins

4.2.8.1 Chemistry, Occurrence and Toxicity

Lectins are high molecular weight proteins with agglutinating and mitogenic properties. Lectins bind to plasma proteins, with specificity towards D-galactose, possess some

cytotoxic activity, and have caused macroscopic lesions in rats (e.g. ascites, congested intestine, pancreatic haemorrhages) (Bloksma et al, 1982; Pusztai, 1991). Viscotoxins are low molecular weight proteins with cardiotoxic properties.

4.2.8.2 Mistletoe (*Viscum album*)

Mistletoe consists of the leaf, fruit (berry) or twig of the parasitic plant *Viscum album*. Traditionally it has been used for its reputed hypotensive, cardiac depressant, and sedative properties (Newall et al, 1996). Mistletoe contains a mixture of high molecular weight polypeptides, quoted molecular weights including 160 000, 115 000, and 60 000 (Luther et al, 1980; Ziska et al, 1978 & 1979). Mistletoe also contains a mixture of low molecular weight polypeptides including the pure viscotoxins A_2, A_3, and B (Olson, 1974; Samuelsson, 1973; Samuelsson & Jayawardene, 1974).

Toxic actions in animals have been documented for mistletoe lectins and viscotoxins. Agglutinating activity for mistletoe lectins has been observed with a number of cells including erythrocytes (non-specific to blood type), lymphocytes, leucocytes, macrophages, glycoproteins, and plasma proteins (Franz et al, 1981; Luther et al, 1980; Ziska et al, 1978) Mistletoe lectins inhibit protein synthesis in both cells and cell-free systems (Stirpe et al, 1980). Cardiotoxic actions have been documented for the viscotoxins, as well as toxic effects on smooth and skeletal muscle (Andersson & Johannsson, 1973; Rosell & Samuelsson, 1966).

Symptoms of toxicity documented following the ingestion of mistletoe include hypotension, coma, seizures, myosis, mydriasis, and death (Hall et al, 1986). Mistletoe berries are only permitted to be sold through pharmacies (Anon, 1977). Mistletoe herb is not listed on the GSL (Anon, 1984b), and it is advised that the herb should only be prescribed by a registered herbal practitioner (Mabey, 1988)

4.2.8.3 Pokeroot (*Phytolacca americana*)

Pokeroot refers to the root of the plant *Phytolacca americana*. Traditionally, pokeroot has been used to treat rheumatism, pharyngeal/respiratory infections, and skin infections (Newall et al, 1996). Pokeroot contains lectin constituents known as Pokeweed Mitogen (PWM). PWM consists of five glycoproteins Pa^{-1} - Pa^{-5}, reported to possess a mixture of agglutinating and non-agglutinating activities affecting both T-cell and B-cell lymphocytes (McPherson, 1979). All parts of the pokeroot plant are considered as potentially toxic, with the root generally recognised as the most toxic part (Roberge et al, 1986). Toxicity is reported to increase with plant maturity although the young green berries are more toxic compared to the more mature red fruits (Roberge et al, 1986). Haematological aberrations have been observed in human peripheral blood following oral ingestion of the berries or exposure of broken skin/conjunctival membrane to the berry juice (Barker et al, 1965, 1966, 1967) In 1979, the American Herb Trade Association declared that pokeroot should no longer be sold as a herbal beverage or food (Tyler et al, 1981). It further recommended that all packages containing pokeroot carry an appropriate warning regarding the potential toxicity of pokeroot when taken internally. In the UK, manufacturers of licensed medicinal products are permitted to include pokeroot provided that the dose is restricted and that suitable evidence is given to demonstrate the absence of the toxic protein constituents (Newall et al, 1996)

4.2.9 Saponins

4.2.9.1 Chemistry, Occurrence, Toxicity

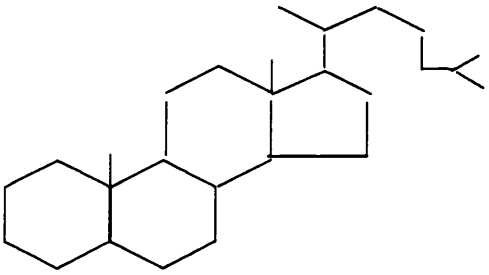
Saponins are high molecular weight compounds that exist naturally as glycosides, acid hydrolysis yielding an aglycone (sapogenin) and various sugars and uronic acids (Hostettmann & Marston, 1995) . Two structural types of sapogenin are recognised: steroidal (usually tetracyclic triterpenoids) and a pentacyclic triterpenoid type (Figure 4.12). Steroidal saponins are less well distributed in nature than the pentacyclic triterpenoid type. Well known examples of steroidal saponins are the cardiac glycoside digitonin (from *Digitalis purpurea* and *D.lanata*), and dioscin (from the yam,

Dioscorea spp.) which is used as the starting material in the partial synthesis of steroidal compounds. Plant families known to contain steroidal saponins include Dioscoreaceae, Amaryllidaceae, Liliaceae, Leguminosae and Solanaceae. Three structural types of pentacyclic triterpenoid exist based on α-amyrin, β-amyrin and lupeol (Figure 4.13) (Evans, 1996). Examples of plants used in herbal remedies that contain triterpenoid saponins include horsechestnut (*Aesculus hippocastanum*), calendula (*Calendula officinalis*), liquorice (*Glycyrrhiza* spp.), pokeroot (*Phytolacca americana*) and primula (*Primula* spp.). Saponins are well known for their detergent properties, and from a toxicological point of view for their haemolytic properties. Haemolytic saponins are highly toxic when given intravenously, although their acute toxicity is low when given orally. This has been attributed to limited absorption across the intestinal mucosa. It has been noted that haemolytic saponins interact with and permeabilise the brush-border membrane of the intestinal absorptive cells, resulting in a marked reduction in the transport of nutrients and in an increased cell turnover. As a result of these physiological actions, saponins may facilitate the systemic entry of substances normally excluded by the gut. The low toxicity of orally ingested saponins to man has been suggested to be primarily due to the large surface area of the gastro-intestinal tract in relation to the concentration of saponins to which it is exposed (Price et al, 1987). Oral ingestion of saponins may cause irritation of the gastro-intestinal mucosa (see Pokeroot below).

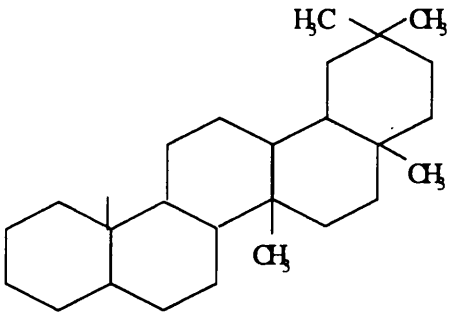
4.2.9.2 Horsechestnut (*Aesculus hippocastanum*)

Horsechestnut is represented by the seed of *Aesculus hippocastanum*. Traditionally it has been used for peripheral vascular disorders such as varicose veins, haemorrhoids and phlebitis, diarrhoea, fever, and enlargement of the prostate gland (Newall et al, 1996). Horsechestnut contains a mixture of triterpenoid saponins collectively referred to as aescin. The effect of aescin, both free and albumin-bound, on renal tubular transport processes has been studied in the isolated, artificially perfused frog kidney (Rothkopf et al, 1977). It was found that aescin primarily affects tubular, rather than glomerular,

Figure 4.12 Steroidal and Pentacyclic Saponins

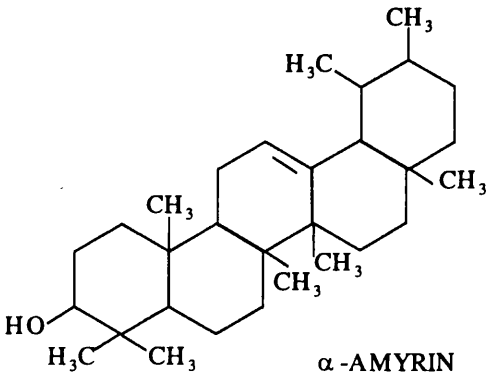


STEROIDAL SAPOGENIN

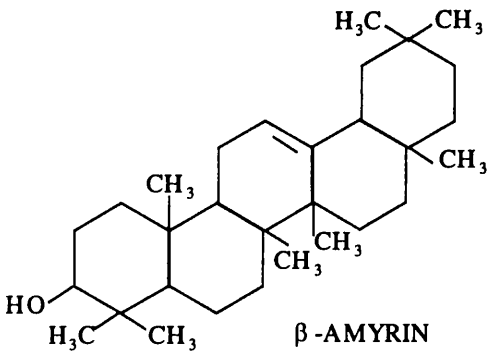


PENTACYCLIC SAPOGENIN

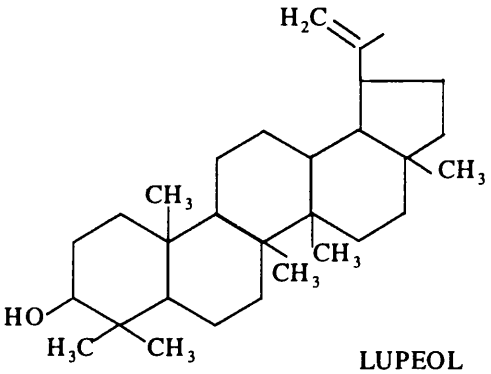
Figure 4.13 α-Amyrin, β-amyrin, Lupeol



α -AMYRIN



β -AMYRIN



LUPEOL

epithelium and that binding of aescin to plasma protein (approximately 50%) protects against this nephrotoxicity. Clinically, the nephrotoxic potential of aescin is thought to present a real risk in existing renal damage or where there is displacement from plasma protein binding (Rothkopf et al, 1977). Two incidences of human nephropathy secondary to the ingestion of high doses of aescin have been reported (Grasso & Corvaglia, 1976)

4.2.9.3 Pokeroot (*Phytolacca americana*)

Pokeroot, represented by the root of *Phytolacca americana*, contains various triterpenoid saponins referred to as phytolaccosides (Newall et al, 1996). All parts of the plant are considered as potentially toxic, with the root generally regarded as the most toxic part. The toxicity of pokeroot is attributed to the lectin (see 4.2.8.3) and saponin constituents. The latter are irritant to mucous membranes and severe gastrointestinal symptoms, such as abdominal cramps, prolonged vomiting and profuse diarrhoea have been reported following pokeroot ingestion (Lewis & Smith, 1979; Roberge et al, 1986).

4.3 Adverse Effects of Herbal Ingredients

The potential for herbal remedies to cause adverse effects is well recognised (Buurma et al, 1983; Buurma & Vulto, 1984; D'Arcy, 1991; DeSmet, 1992& 1995; DeSmet et al, 1992 & 1993; Dukes, 1977, 1980; Penn, 1981, 1982; Saxena, 1985). A survey of enquiries received by the Medical Toxicology Unit (MTU) (formerly the National Poison's Unit) at Guy's Hospital concerning exposure to traditional medicines and food supplements highlighted this potential (Perharic et al, 1994a; Shaw et al, 1996), and resulted in a request by the MTU to receive reports on suspected adverse reactions to traditional medicines and food supplements (Perharic et al, 1994b)

Table 4.7 Examples of Adverse Effects that may occur with Herbal Ingredients

Potential Adverse Effect	Constituent: Herbal Ingredient
Allergic	
Hypersensitive	Sesquiterpene lactones: arnica, chamomile, feverfew, yarrow
Phototoxic	Furanocoumarins: angelica, celery, wild carrot
Immune	Canavanine: alfalfa
Cardiac	Cardiac glycosides: pleurisy root, squill
Endocrine	
Hypoglycaemic	Alfalfa, fenugreek
Hyperthyroid	Iodine: fucus
Hormonal	
Mineralocorticoid	Triterpenoids: liquorice
Oestrogenic	Isoflavonoids: alfalfa, red clover
	Saponins: ginseng
Anti-androgen	Saw palmetto
Irritant	
Gastrointestinal	Numerous compounds including anthraquinones (purgative), capsaicinoids, diterpenes, saponins, terpenoid-rich volatile oils
Renal	Aescin: horse-chestnut; terpenoid-rich volatile oils
Toxic	
Hepatotoxic/ carcinogenic	Pyrrolizidine alkaloids: comfrey, liferoot; β-asarone: calamus
	Lignans: chaparral
	Safrole: sassafras
Mitogenic	Proteins: mistletoe, pokeroot
Cyanide poisoning	Cyanogenetic glycosides: apricot
Convulsant	Camphor/thujone-rich volatile oils

Table 4.7 lists some categories of potential adverse effects and the associated herbal ingredient or constituent. Some of the adverse effects are attributable to toxic constituents of the herb (see Section 4.2), whereas other adverse effects can be associated with the pharmacological actions of the constituents. Many herbal ingredients are irritant and this is commonly attributed to the essential oil. Phenolic components of essential oils are particularly irritant. Generally, it is advisable to avoid excessive or prolonged ingestion of a herb.

4.3.1 Excessive ingestion

Ginseng A wide range of pharmacological activities have been documented for ginseng (*Panax* spp. , *Eleutherococcus senticosus*) and many guidelines have been drawn up in China, Japan and Russia regarding its use. Traditional recommendations for ginseng use have differentiated between short-term for young and healthy individuals, and long-term use for the elderly and sick (Newall et al, 1996). In the short-term, ginseng has been used to improve stamina, concentration, healing process, stress resistance, vigilance and work efficiency. Treatment courses last approximately 15-20 days with a root-free period of approximately two weeks between consecutive courses. In the long-term, ginseng has been used to improve well-being in debilitated and degenerative conditions. When used appropriately, ginseng appears to be relatively non-toxic and most documented side-effects are associated with inappropriate use when compared with traditional warnings and guidelines. In 1979, two studies referred to a Ginseng Abuse Syndrome (GAS) which emphasised that most side-effects documented for ginseng were associated with the ingestion of large amounts of ginseng together with other psychomotor stimulants, including tea and coffee. Traditionally, it is recommended that ginseng should not be taken with stimulants, including coffee (Baldwin et al, 1986). GAS was defined as diarrhoea, hypertension, nervousness, skin eruptions and sleeplessness. Other symptoms occasionally observed included amenorrhoea, decreased appetite, depression, euphoria, hypotension and oedema. The GAS studies were subsequently criticised over the variety of ginseng and other

preparations used, and over the lack of authentication of ginseng species. Symptoms of overdose that have been reported elsewhere are described as those exhibited by individuals allergic to ginseng, namely palpitations, insomnia and pruritus, together with heart pain, decrease in sexual potency, vomiting, haemorrhagic diathesis, headache and epistaxis; ingestion of very large doses have even reported to be fatal (Baranov, 1982). Excessive doses of ginseng have been reported to cause agitation, insomnia, and raised blood pressure and have been referred to as abuse of the remedy.

Liquorice The corticosteroid effects of liquorice (*Glycyrrhiza glabra*) are well known and are attributed to the triterpenoid constituents. Excessive or prolonged liquorice ingestion has resulted in symptoms typical of primary hyperaldosteronism, namely hypertension, sodium, chloride and water retention, hypokalaemia and weight gain, but also in low levels of plasma renin activity, aldosterone and antidiuretic hormone (Chamberlain, 1970; Conn et al, 1968; Forslund et al, 1989). Individuals consuming vastly differing quantities of liquorice have exhibited similar side-effect symptoms, indicating that the mineralocorticoid effect of liquorice is not dose dependent and is a saturable process (Corrocher et al, 1983). Hypokalaemic myopathy has also been associated with liquorice ingestion (Bannister et al, 1977; Cibelli et al, 1984; Heidermann & Kreuzfelder, 1983; Piette et al, 1984; Ruggeri et al, 1985) Severe hypokalaemia with rhabdomyolysis was documented in a male patient following the ingestion of an alcohol-free beverage containing only small amounts of glycyrrhetinic acid (0.35g/day) (Piette et al, 1984). The patient had known liver cirrhosis due to alcohol consumption and it was suggested that cirrhotic patients may be more susceptible to the mineralocorticoid side-effects of liquorice (Piette et al, 1984). Other adverse effects reported with liquorice include severe congestive heart failure and pulmonary oedema in a man who had ingested 700g liquorice over eight days (Chamberlain, 1970), amenorrhoea (anti-oestrogenic action) (Corrocher et al, 1983), and hyperglycaemia and hypokalaemia-induced myopathy (Jamil et al, 1986). Symptoms of hyperaldosteronism often resolve quickly, within a few days to a few weeks, even in individuals who have ingested liquorice for many years (Mantero, 1981).

Parsley Chronic and excessive consumption of fresh parsley (170g/day for 30 years) has been associated with generalised itching and pigmentation of the lower legs in a 70 year old woman (Cootes, 1982). The symptoms were attributed to excessive ingestion of parsley in the presence of chronic liver disease. The aetiology of the chronic hepatitis was unknown, but considered possibly related to chronic exposure to the furanocoumarin constituents in parsley. Apiole, a major component in parsley essential oil, is known to be toxic and may also have contributed to the chronic liver disease.

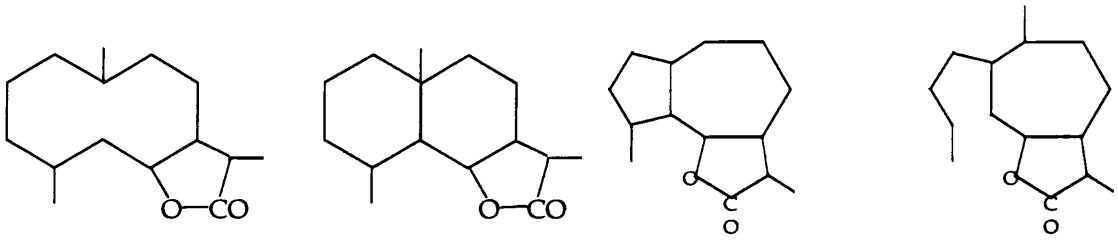
4.3.2 Hypersensitivity Reactions

4.3.2.1 Sesquiterpene Lactones

Sesquiterpene lactones are common constituents of most genera of the Compositae, and have been reported to occur sporadically in genera of various other plant families. The major structural types of sesquiterpene lactones are germacranolides, guaianolides, pseudoguaianolides, eudesmanolides and xanthanolides (Figure 4.14) (Rodriguez et al, 1976). Sesquiterpene lactones from species of Compositae, Frullaniaceae, Lauraceae and Magnoliaceae families have been shown to be a major class of allergens causing allergic contact dermatitis in humans. The presence of an exocyclic alpha-methylene-γ-lactone group is recognised as an immunochemical prerequisite for allergenic activity. It is considered that this group may conjugate with sulphydryl groups of proteins in cells to form complete antigens capable of producing cell-mediated contact allergic reactions (Rodriguez et al, 1976). Cross-reactivities have been reported between species botanically related in the same family (e.g. arnica, chamomile, dandelion, feverfew, tansy, and yarrow) or between chemically-related (sesquiterpene lactone) species from other plant families such as Frullaniaceae, Lauraceae and Magnoliaceae (Corres, 1984; Hausen, 1979; Schmidt, 1986). In view of the cross-reactivities, individuals with an existing hypersensitivity to a sesquiterpene lactone-containing plant should avoid contact with species from all other plant families known to contain sesquiterpene lactones (Hausen & Osmundsen, 1983). This should include the use of soaps, cosmetics,

shampoos, bath oils, herbal sweets etc. containing arnica, chamomile or other herbs, as well as plant tinctures (such as arnica) to self-treat soft-tissue injuries (Hausen, 1979).

Figure 4.14 **Main Sesquiterpene Lactone Structural Types**



Germacranolide Eudesmanolide Guaianolide Xanthanolide

Herbs commonly used in herbal remedies that contain allergenic or potentially allergenic sesquiterpene lactones are arnica, artichoke, boneset, chamomile, dandelion, elecampane, feverfew, holy thistle, tansy, wild lettuce and yarrow. Allergic contact dermatitis has been reported for many of the herbs and the allergenic sesquiterpene lactone identified, for example alantolactone (elecampane), anthecotulid (chamomile), cynaropicrin (artichoke), and parthenolide (feverfew) (Newall et al, 1996).

4.3.3 Phototoxic Reactions

As discussed under Section 4.2.9, furanocoumarins are compounds that use sunlight to elicit a toxic reaction on the skin. Phototoxic reactions have been associated with herbs known to contain furanocoumarin constituents.

4.3.3.1 Angelica (*Angelica archangelica*)

Both angelica (*Angelica archangelica*) and the root oil have been reported respectively to cause photodermatitis and phototoxicity, following external contact (Duke, 1985;

Frohne & Pfander, 1984; Opdyke, 1975; Tisserand & Balacs, 1996). The phototoxicity of angelica is primarily attributable to bergapten.

4.3.3.2 Celery (*Apium graveolens*)

Celery (*Apium graveolens*) seed (not the stem) is used in herbal remedies and contains a number of furanocoumarin constituents including bergapten, although no reports of phototoxic reactions have been documented. Photosensitivity reactions following external contact (Austad & Kavli, 1983; Berkley et al, 1986; Reynolds, 1982) , and allergic and anaphylactic reactions following oral ingestion (Dechamp et al, 1984; Forsbeck & Ros, 1979) of celery stems have, however, been reported. The photosensitivity reactions have been attributed to the furanocoumarin constituents, the levels of which are reported to increase considerably in diseased stems (Ashwood-Smith et al, 1985; Chaudhary et al, 1985). Allergic reactions to celery are thought to be mediated by IgE antibodies and an association between pollen and celery allergy has been postulated, although the common antigen has not been determined (Pauli et al, 1985). Cross-sensitivities to celery have been documented in patients with existing allergies to dandelion and wild carrot (Mitchell & Rook, 1979).

4.3.3.3 Parsley (*Petroselenium crispum*)

Parsley contains furanocoumarin constituents including bergapten. However, ingestion of parsley in amounts normally used in foods is unlikely to cause a phototoxic reaction in view of the negligible amounts of bergapten provided (Zaynoun et al, 1985). Excessive ingestion of parsley has been associated with a phototoxic reaction together with hepatotoxicity (see Section 4.3.1). A phototoxic reaction following topical contact with parsley is possible.

4.4 Potential Interactions in Specific Therapeutic/Patient Groups

One of the ways in which the health risks associated with a licensed medicine can be minimised is to highlight its possible side-effects and interactions, and to contra-indicate its use in certain patient groups considered more susceptible to certain side-effects. All licensed medicines possess a summary of product characteristics in which this information is stated. Furthermore, all licensed medicines now have to include a patient information leaflet in which information about the medicine, including warnings of possible side-effects, interactions and contra-indications, is provided to the patient. The continuous post-licensing safety assessment of medicines carried out by the Medicines Control Agency often results in an updating of a medicines side-effect profile and warnings section, as more is learnt about the use of a medicine within an increasing patient population.

Limited information has been documented concerning the interaction of herbal remedies with conventional medicines (Anderson & Phillipson, 1985; D'Arcy, 1993; Newall et al, 1996). Instances of drug interactions have been tentatively linked, retrospectively, to the concurrent use of herbal remedies, although the rationale for such interactions is often difficult to justify if knowledge regarding the pharmacological activity of the herbal remedy is in question. An attempt can be made, however, to identify herbal ingredients that have the potential to interfere with specific categories of conventional drugs, based on known phytochemical and pharmacological properties of the herb, and on any documented side-effects.

For example, herbs containing substantial levels of coumarins may potentially increase blood coagulation time if taken in large doses. St John's Wort contains hypericin, a known photosensitiser, and celery and parsley contain furanocoumarins which may also precipitate a photosensitive reaction. In addition, concomitant ingestion of a conventional medicine associated with photosensitive reactions (e.g. amiodarone) and of a furanocoumarin-containing herb may increase the risk of developing a phototoxic reaction. Some herbs, such as juniper, sage, tansy and yarrow, contain irritant volatile oils and may be toxic if ingested in large quantities. Prolonged or excessive use of a herbal diuretic may potentiate existing diuretic therapy, interfere with existing hypo/hypertensive therapy, or potentiate the effect of certain cardioactive drugs due to

hypokalaemia. Herbs which have been documented to lower blood sugar levels may cause hypoglycaemia if taken in sufficient amounts or interfere with existing hypoglycaemic therapy. An individual receiving antihypertensive therapy may be more susceptible to the hypertensive side-effects that have been documented with, for example, ginseng or which are associated with the excessive ingestion of liquorice.

This approach has been used in drawing up Appendixes 1-13 (Newall et al, 1996). These Appendixes provide information on potential drug herb interactions. Appendix 1 groups together various therapeutic categories of medical drugs that may be affected by a particular herb or group of herbs. Appendixes 2-13 alphabetically list examples of herbal ingredients which are reported to have a specific activity, namely, laxative, cardioactive, diuretic, hypotensive and hypertensive, antcoagulant and coagulant, hypolipidaemic and hyperlipidaemic, hormonal, immunostimulating, allergenic and irritant. Some commonly occurring groups of natural products found within herbal ingredients contribute towards their activities, toxicities or adverse effects. Appendixes 14-20 list examples of herbal ingredients which contain amines, alkaloids or which have sympathomimetic activity, coumarins, flavonoids, iridoids, saponins, tannins or volatile oils (Newall et al, 1996).

Table 4.8 is derived from Appendixes 1-13, and gives examples of herbal ingredients that may potentially interact with conventional medicines.

Table 4.8 Potential Drug/Herb Interactions

Drug/Therapeutic Category	Herbal Ingredient Interacting	Comment	Possible Effect
Allergic conditions	Celery, parsley	Furanocoumarins	Risk of phototoxic reaction

Drug/Therapeutic Category	Herbal Ingredient Interacting	Comment	Possible Effect
	Chamomile, feverfew, tansy	Sesquiterpene lactones	Risk of allergic reaction
Terfenadine	Cardioactive herbal ingredients e.g. broom, figwort	-	May increase arrhythmogenic potential of terfenadine
	Diuretic herbal ingredients, e.g. agrimony, dandelion, shepherd's purse	Risk of hypokalaemia	Electrolyte imbalance may increase arrhythmogenic potential of terfenadine
Anticoagulant therapy	Asafoetida Northern Prickly Ash	Coumarin constituents	Potentiation
Antidiabetic therapy	Devil's Claw Elecampane	Hypo/hyper- glycaemic activity	Interference with therapy
Antihypertensive therapy	Ginseng Hawthorn Horsechestnut	Hyper/hypotensive Hypotensive Hypertensive	Interference with therapy
Antipsychotics	Evening Primrose	-	Potential risk of seizure
Cardiac disorders, cardiac glycosides	Figwort Pleurisy Root, Uva-ursi	Cardioactive glycosides Diuretic, hypokalaemia	Potentiation Increased risk of toxicity
Corticosteroid	Bayberry,	Corticosteroid activity	Potentiation;

Drug/Therapeutic Category	Herbal Ingredient Interacting	Comment	Possible Effect
therapy	Liquorice		increased risk of side-effects
Diuretics	Agrimony, dandelion, shepherd's purse	Diuretic activity	Potentiation; increased risk of hypokalaemia
Sex hormones	Ginseng	Oestrogenic activity	Interference with therapy

4.5 Pregnancy and Lactation

Few conventional medicines have been established as safe to take during pregnancy and it is generally recognised that no drug substance should be taken unless the perceived benefit outweighs the possible risk. This rule is also applicable to herbal remedies which are often mistakenly considered to be natural and completely safe alternatives to conventional medicines.

A drug substance taken by a nursing mother presents a hazard if it is transferred to the breast milk in pharmacologically or toxicologically significant amounts. Limited information is available regarding the safety of conventional medicines taken during breastfeeding. Much less information exists for herbal ingredients and generally the use of herbal remedies is not recommended during lactation.

Table 4.9 lists some examples of herbal ingredients that are best avoided during pregnancy (Newall et al, 1996). As with conventional medicines, no herbal remedy should be taken during pregnancy unless the benefit outweighs the potential risk. The potential health risk involved with ingesting an unlicensed herbal preparation is of even greater significance during pregnancy and lactation. It is essential that if used, a herbal preparation is of suitable quality and the herbal ingredients are known. A foetus may

well be more susceptible to the toxic effects/constituents of a herb than the ingesting mother. An instance of fatal hepatotoxicity in a newborn child whose asymptomless mother had consumed a herbal expectorant tea during pregnancy highlights this (Roulet et al, 1988). The tea was found to contain pyrrolizidine alkaloids.

Table 4.9 Herbal Ingredients Best Avoided or Used with Caution During Pregnancy

Herb	Effect	Herb	Effect
Agnus castus	Hormonal action	Devil's Claw	Documented as oxytocic
Aloes	Cathartic; reputed abortifacient	Euphorbia	Smooth muscle activity, *in vitro*
Apricot	Cyanide toxicity	Fenugreek	Uterine stimulant *in vitro*, reputed oxytocic
Blue Flag	Irritant oil	Feverfew	Reported to cause abortion in cattle, uterine contractions in full-term women; reputed abortifacient and to affect the menstrual cycle
Bogbean	Irritant, possible purgative	Frangula	Anthraquinones, avoid non-standardised preparations
Boldo	Irritant oil	Fucus	Thyroid gland activity; possible toxic metal contamination
Boneset	Cytotoxic constituents (related species)	Ginseng, Eleuthero-coccus	Hormonal activity
Borage	Pyrrolizidine alkaloid toxicity	Ginseng, Panax	Hormonal activity
Broom	Sparteine, oxytocic	Golden Seal	Uterine stimulant *in vitro*
Buchu	Irritant oil	Ground Ivy	Irritant oil
Burdock	Uterine stimulant, *in vivo*	Hawthorn	Uterine activity *in vivo* &

Herb	Effect	Herb	Effect
			in vitro
Calendula	Uterine stimulant *in vitro*; reputed to affect the menstrual cycle	Hops	Uterine activity *in vitro*
Cascara	Anthraquinones, avoid non-standardised preparations	Horehound White	Uterine stimulant in animals; reputed abortifacient and to affect menstrual cycle
Chamomile German	Uterine stimulant in-vitro; reputed to affect the menstrual cycle	Horseradish	Irritant oil
Chaparral	Uterine activity, hepatotoxic	Hydrocotyle	Uterine relaxant *in vitro*; reputed abortifacient and to affect menstrual cycle
Cohosh, Black	Uterine oestrogen receptor binding *in vitro*	Jamaica Dogwood	Uterine activity *in vivo* & *in vitro*; irritant
Cohosh, Blue	Antifertility and uterine stimulant *in-vitro*; reputed abortifacient and to affect the menstrual cycle	Juniper	Uterine stimulant *in vivo*; reputed abortifacient and to affect menstrual cycle
Cola	Caffeine, restrict consumption	Liferoot	Pyrrolizidine alkaloid toxicity
Coltsfoot	Pyrrolizidine alkaloid toxicity	Liquorice	Oestrogenic & steroid activity; reputed abortifacient
Comfrey	Pyrrolizidine alkaloid toxicity	Lobelia	Lobeline, toxicity
Cornsilk	Uterine stimulant *in vivo*	Mate	Caffeine, restrict

Herb	Effect	Herb	Effect
			consumption
Damiana	Cyanogenetic glycosides; avoid high doses	Meadow-sweet	Salicylates; expression in breastmilk may cause rashes in babies; uterine activity *in vitro*
Mistletoe	Toxic constituents, uterine stimulant animal studies	Rhubarb	Anthraquinones, avoid non-standardised preparations
Motherwort	Uterine activity *in vitro*; reputed to affect the menstrual cycle	Sage	Toxic oil (thujone)
Nettle	Uteroactivity *in vivo*; reputed abortifacient and to affect the menstrual cycle	Sassafras	Toxic (safrole)
Parsley	Avoid excessive ingestion, apiole in oil	Saw Palmetto	Anti-androgen and oestrogenic activities
Passion flower	Uterine stimulant, animal studies	Scullcap	Potential hepatotoxicity (*Teucrium*); traditional use to eliminate afterbirth and promote menstruation
Pennyroyal	Toxic oil (pulegone)	Senna	Anthraquinones, avoid non-standardised preparations
Plantain	Uterine activity *in vitro*	Shepherd's Purse	Uterine stimulant in vitro; reputed abortifacient and to affect the menstrual cycle

Herb	Effect	Herb	Effect
Pleurisy Root	Uterine activity *in vivo*; cardioactivity	Squill	GI irritant (emetic); reputed abortifacient and to affect the menstrual cycle
Pokeroot	Toxic constituents, uterine stimulant in animals, reputed to affect the menstrual cycle	St. John's Wort	Uterine activity *in vitro*
Poplar	Salicylates; expression in breastmilk may cause rashes in babies	Tansy	Toxic oil (thujone); uterine activity in animals
Prickly Ash, Northern	Pharmacologically active constituents	Uva Ursi	Oxytocic (large doses)
Prickly Ash, Southern	Pharmacologically active constituents	Vervain	Uteroactivity *in vivo*; reputed abortifacient & oxytocic
Pulsatilla	Uterine activity *in vivo* & *in vitro*; reputed to affect the menstrual cycle; fresh plant irritant	Wild Carrot	Oestrogenic activity; irritant oil
Queen's Delight	Irritant diterpene constituents	Willow	Salicylates; expression in breastmilk may cause rashes in babies
Raspberry	Uterine activity *in vitro*; traditional use in labour	Yarrow	Oil contains thujone; reputed abortifacient
Red Clover	Oestrogenic activity	Yellow Dock	Anthraquinones, avoid non-standardised preparations

Herbs listed in Table 4.9 are included for a variety of reasons, some of which are discussed below:

Toxicity Herbs that contain known toxic constituents should obviously not be taken during pregnancy. Herbs that fall into this category include apricot, boneset, borage, broom, chaparral, coltsfoot, comfrey, damiana, liferoot, lobelia, mistletoe, pokeroot, prickly ash, queen's delight, sassafras, and scullcap.

Volatile Oils Many herbs are reputed to be abortifacient and for some this reputation can be attributed to their volatile oil. However, only two volatile oil components have been reported as abortifacient, apiole contained in parsley seed and leaf oils, and sabinyl acetate present in sage oil (Tisserand & Balacs, 1995). Interestingly, a spasmolytic action on the isolated human uterus and fallopian tubes has been documented for juniper, pennyroyal, rue, savin and tansy oil (Gunn, 1921). The author commented that the absence of a stimulant effect on the uterus from these traditional emmenagogue oils results in larger, potentially toxic, amounts being ingested. Indeed, many volatile oil components are toxic, rather than abortifacient, and it is this toxicity that results in an abortion rather than an abortifacient action. For example, fatalities have been reported following the ingestion of pennyroyal oil as an abortifacient, with the doses required for an abortifacient effect also causing nephrotoxicity and hepatotoxicity (Gunby, 1979; Opdyke, 1974a; Sullivan et al, 1979; Vallance, 1955). Pennyroyal oil contains pulegone, a known hepatotoxic ketone compound. Sage and tansy herbs are traditionally reputed to be abortifacients. Both herbs contain another toxic ketone, thujone, in their volatile oil. An alcoholic extract of juniper berries has exhibited an abortifacient effect (Agrawal et al, 1980), although the activity is not attributable to the volatile oil as commonly believed (Tisserand & Balacs, 1995). This may stem from a common confusion between juniper (*Juniperus communis*) and savin (*Juniperus sabina*), which does contain an abortifacient constituent (sabinyl acetate) in its volatile oil (Tisserand & Balacs, 1995). Many herbs contain irritant volatile oils (usually attributable to oxygenated terpene components) which may irritate the genito-urinary tract, cause congestion, and may induce reflex uterine contractions.

Uteroactivity A stimulant or spasmolytic action on uterine muscle has been documented for some herbs including blue cohosh, burdock, fenugreek, golden seal, hawthorn, jamaica dogwood, motherwort, nettle, raspberry and vervain. Many of these actions are observed either in isolated preparations or *in-vivo*, and their clinical relevance is difficult to establish. However, unless the perceived benefit of taking the herb outweighs this potential risk, the use of such herbs during pregnancy is either best avoided or done so with extreme caution. Raspberry is a popular herbal remedy taken during pregnancy to help promote an easier labour by relaxing uterine muscles. The pharmacological activity exhibited by raspberry may vary between preparations and from one individual to another. It would not seem wise to use raspberry during pregnancy without first obtaining medical advice.

Some stimulant laxative preparations are licensed for use during pregnancy (e.g. Senokot), but the use of unstandardised herbal preparations should generally be avoided as their pharmacological effect may be unpredictable. Hormonal activity has been documented for a number of herbs (e.g. agnus castus, black cohosh, ginseng, liquorice, red clover, saw palmetto, and wild carrot), which are therefore best avoided during pregnancy.

A number of herbs (e.g. asafoetida, avens, gentian, horehound black, myrrh, skunk cabbage) not listed in Table 4.9 are traditionally reputed to affect the menstrual cycle and/or act as abortifacients, although no documented phytochemical or pharmacological evidence supports this reputation. Caution is obviously advisable in the use of such herbs. Furthermore, for other herbs (e.g. bayberry, burnet, cereus, clivers, false unicorn, gravel root, hydrangea, lady's slipper, parsley piert, pilewort, stone root) very little is known regarding their chemistry, pharmacology and toxicity. These herbs are therefore best avoided during pregnancy.

4.6 Herbal Teas

An increased awareness of the harmful effects associated with excessive tea and coffee consumption has prompted many individuals to switch to herbal teas, in an attempt to reduce their caffeine and tannin consumption. In particular, individuals with peptic ulcers, hypertension, and other cardiovascular and nervous disorders are advised to give up tea and coffee. Whilst some herbal teas may offer pleasant alternatives to tea and coffee, some contain herbs with pharmacologically and/or toxicologically significant constituents. Most herbal teas are crude complex mixtures which are neither uniformly prepared nor assayed for purity. In the US, a herbal tea with ingredients listed as decocainised coca leaves was found to contain levels of cocaine normally present in the plant together with contaminant fragments of a tree grown adjacent to coca (Siegal et al, 1986). Atropine poisoning associated with a commercially packaged burdock root tea was attributed to contamination of the tea with a herbal source of Solanaceous alkaloids, possibly belladonna leaf (Bryson et al, 1978).

A survey of herbal teas available in London in 1987, revealed more than 100 different teas involving some 117 different herbs (Baldwin et al, 1987). The teas were single or multi-herb preparations, mainly available as teabags but in some cases as the loose plant material. The popular herbs, hibiscus, rosehip, orange, chamomile, peppermint, blackberry, chicory, lemongrass and apple, are all considered to be safe and many are legally classified in the US as GRAS (Generally Regarded as Safe). However, claims that herbal teas are low in caffeine and tannin, or indeed free from these constituents, are not necessarily true since some herbs contain substantial levels of caffeine (e.g., mate) or tannin (e.g. bayberry, blackberry, mate, peppermint, raspberry, uva-ursi, yellow dock) (Baldwin et al, 1987b; Morton, 1986). The high tannin content in some herbal ingredients of teas has been associated with their potential carcinogenicity (Morton, 1986).

In addition to caffeine and tannin, many potentially toxic herbs have been reported as ingredients of herbal teas in the UK and US, and are listed in Table 4.10 (Baldwin et al, 1987b; Ridker et al, 1987). Many of the herbs listed in this table have already been

referred to under section 4.2, such as comfrey, pokeroot, sassafras and tansy ragwort (*Senecio*). Other herbs listed contain pharmacologically active constituents such as alkaloids and coumarins. Accidental digitalis poisoning (sometimes fatal) has been reported following the self-collection of foxglove leaves instead of comfrey leaves for a herbal tea (Ridker, 1987). Foxglove ingestion results in immediate signs of toxicity, but in view of the pyrrolizidine alkaloid constituents in comfrey, the use of either plant is associated with a health risk.

Table 4.10 Potentially Toxic Ingredients of Commercial Herbal Teas available in the UK[1] and US[2]

Herbal Ingredient	Potential Toxic Effect
Buckthorn[2]	Anthraquinones, purgative
Chamomile[1,2]	Allergic reaction
Comfrey[1,2]	Pyrrolizidine alkaloids, hepatotoxic
Eucalyptus[1]	Irritant essential oil
Feverfew[1]	Allergic reaction
Ginseng[1]	Numerous pharmacological activities, including oestrogenic
Gordolobo (*Senecio* sp.)[2]	Pyrrolizidine alkaloids, hepatotoxic
Groundsel (*Senecio* sp.)[2]	Pyrrolizidine alkaloids, hepatotoxic
Hawthorn berries[1]	Cardiotonic
Horsetail[1]	Toxic to livestock, thiaminase
Juniper berries[1]	Abortifacient (extract), irritant volatile oil,
Larkspur[1]	Toxic aconite-type alkaloids
Liquorice[1]	Corticosteroid-type action
Lobelia[2]	Lobeline
Nutmeg[2]	Myristicin, potential hallucinogenic effect
Pennyroyal[1]	Pulegone in essential oil, hepatotoxic

Herbal Ingredient	Potential Toxic Effect
Pokeroot[2]	Toxic lectins (pokeweed mitogens), saponins
Sassafras[2]	Safrole in essential oil, carcinogenic, hepatotoxic
Senna[1,2]	Anthraquinones, purgative
Tansy ragwort (*Senecio* sp.)[2]	Pyrrolizidine alkaloids, hepatotoxic
Uva-ursi[1]	Hydroquinone, toxic in large doses
Woodruff[2]	Coumarin constituents
Yarrow[1]	Allergic reaction

[1] Baldwin et al, 1987
[2] Ridker, 1987

This potential toxicity should be of concern to all individuals who use herbal teas, but in particular to pregnant women who may turn to herbal teas as a "healthier" alternative to conventional tea and coffee. In addition, many individuals who turn to herbal teas do so because of an existing medical condition for which they may well be receiving medical treatment. Many herbal teas contain ingredients with pharmacologically significant constituents. There is therefore the potential for herbal teas to interact with concomitant medication, particularly if the herbal tea is consumed in large quantities. The dose of active constituents consumed from herbal teas can vary considerably depending upon the amount of the herb used, the temperature of the water, and the time allowed for the tea to brew. Total consumption will differ depending on the number of cups consumed per day.

When using herbal teas, it would seem advisable to purchase preparations manufactured by well established companies and which clearly state the ingredients on the labelling. Preparations packaged into teabags provide a more standardised dose than loose herbs and are therefore preferable. It is inadvisable to purchase herbal teas as loose plant material since there is no guarantee over the quality of the herbal material. When using herbal teas that contain herbs commonly used in herbal remedies, caution should be

exercised in establishing the pharmacological actions and possible toxicological effects. Many herbal teas contain, for example, laxative ingredients such as cascara, frangula and senna, often in combination. The use of such unstandardised preparations may result in a drastic purgative effect. Chamomile is another common ingredient of herbal teas. Allergic reactions to chamomile, and to other members of the Asteraceae plant family, are well recognised with cross-sensitivities reported (see Section 4.3.2). Any individual with an existing hypersensitivity to any plant, but in particular to a member of the Asteraceae, should avoid herbal teas containing chamomile.

4.7 Discussion

The potential health risks presented by traditional medicines, including herbal remedies, have been recognised for many years and discussed by a number of authors. Poor quality control in the manufacture of a herbal preparation may result in a failure to ensure correct botanical identification and an uncontaminated plant source. Both of these factors may result in a herbal preparation that is hazardous to human health. Quality issues affecting herbal medicines have been discussed in Chapter 3.

Irrespective of the quality of a herbal preparation, there are a number of herbal ingredients which contain toxicologically significant constituents. Determining the safety of a medicine involves a careful assessment of the risk to benefit ratio presented by a specific medicinal product. Assessing the safety of a herbal medicine is no different. In general, herbal remedies are used to treat non-life threatening conditions and therefore the potential risk presented by exposure to known toxic constituents cannot be justified. However when considering the possible risk presented by a herbal drug, it is important to consider the intended level of exposure to a known toxic chemical. The dose of a potentially toxic constituent provided by a particular herbal remedy may be considered low enough so as not to represent a hazard to human health, may require limiting, or may result in banning the herbal ingredient from inclusion in herbal medicines. Pokeroot, for example, is permitted as an ingredient of licensed medicines providing the dose is restricted and the absence of toxic protein constituents

is suitably demonstrated (Newall et al, 1996). Coltsfoot contains potentially toxic unsaturated pyrrolizidine alkaloid (PA) constituents but at a level too low to be considered a risk to human health. Comfrey, which contains greater amounts of unsaturated PA, is not permitted as an ingredient of a licensed medicine or of a formulated food supplement (Newall et al, 1996). The Society for the Promotion of Nutritional Therapy objected to this ban on all capsules and tablets containing comfrey, suggesting that safety concerns may be allayed by cautionary labelling, limits for PA content, and restriction of the sale of comfrey products to trained nutritional therapists and medical herbalists (Anon, 1994b). However, to-date, the voluntary withdrawal of all formulated food supplements containing comfrey remains in place.

Some of the toxicologically significant constituents considered in this chapter are also present in culinary herbs and spices. When assessing the potential health risk presented by the medicinal use of herbs containing these constituents, consideration must be given to the intended therapeutic dose and to the level of constituent in the herb. In the UK, for example, the use of safrole in foods is limited to 1mg/kg. As a minor constituent of many herbs, safrole is not considered to represent a health hazard. However, the use of sassafras in medicines is not permitted due to its high safrole content. β-Asarone is limited to 0.1mg/kg in foods, and only calamus root proven devoid of β-asarone is permitted in medicines.

The traditional use of a herbal remedy, perhaps for many centuries, does not necessarily ensure its safety. The more subtle forms of toxicity such as hepatotoxicity and carcinogenicity may well have been overlooked by previous generations. Recent concerns over the hepatotoxicity of germander and chaparral, both herbs with a traditional medicinal use, have highlighted this fact (Anon 1992a & 1993a; Clark & Reed, 1992; Gordon et al, 1995; Katz & Saibil, 1990). Concern over the potential carcinogenicity of well established anthranoid-containing laxatives, such as senna, frangula, aloe and rhubarb, has prompted the German Federal Institute for Drugs and Medical Devices (BfArM) to impose dose, indication and pack size restrictions on laxatives derived from these herbs (Anon, 1996s).

Formulated products may utilise herbal ingredient preparations such as extracts and tinctures, and combinations of ingredients, that no longer reflect the traditional use of the whole herb. Products combining ginseng and guarana (contains caffeine), for example, oppose the traditional warning that ginseng should not be consumed with stimulants (Shaw et al, 1996). Remedies containing a mixture of Chinese, American and EC herbs are also available (Shaw et al, 1996).

Recent reports by the Medical Toxicology Unit (MTU) at Guy's Hospital (Shaw et al, 1996) and the Consumers' Association (Anon, 1996r) have drawn attention to potential safety hazards associated with the use of traditional remedies and dietary supplements. If anything, the MTU provided some assurance over the use of EC herbs with few serious reactions identified to these remedies. Of more concern were the hepatic reactions associated with the use of traditional Chinese herbal remedies. In light of these reported reactions, the Medicines Control Agency (MCA) has decided to extend the yellow card spontaneous adverse reporting scheme to include unlicensed herbal remedies (Anon, 1996p). This is an important step forward in the pharmacovigilance of herbal remedies within the UK, with the majority being unlicensed and marketed as dietary supplements. Whilst it is recognised that there is always considerable under-reporting in a voluntary reporting scheme, it is important for there to be a single body to whom details of suspected adverse reactions can be submitted. The MTU report also underlined the difficulty in assessing the causality of adverse reactions associated with herbal remedies, often due to a lack of submitted information. Having announced its wish to receive reports of suspected adverse reactions to unlicensed herbal remedies, the MCA will be in an ideal position to rapidly follow-up any serious reports to assist in their evaluation. The Code of Practice recently proposed by the British Herbal Medicine Association (BHMA) includes a commitment to relay any safety related information on unlicensed herbal remedies to the MCA. Hopefully these initiatives will ensure that the MCA remains well informed of any potential safety issues associated with herbal remedies.

5. EFFICACY OF HERBAL REMEDIES

5.1 General Considerations

The medicinal properties of plants have been recognised for centuries and today, 30-40% of all medicines in the UK contain one or more active components derived from flowering plants (Buck, 1996). Only a small percentage of the estimated 250,000-500,000 plant species in the world have been investigated phytochemically and pharmacologically (Hostettmann et al, 1995): it is estimated that approximately 40 species of flowering plants yield all of the known medically-active plant-derived prescription drugs (Buck, 1996). Table 5.1 lists some examples of plant-derived clinically useful drugs. The constant search for clinically useful compounds from plants is highlighted by the relatively recent introduction of Taxol (paclitaxel), licensed for the first line treatment of metastatic carcinoma of the ovary in combination with cisplatin (Anon, 1995c; Anon, 1996b). Taxol is a diterpenoid found in several *Taxus* species including *T.brevifolia* (pacific yew tree) (Wall & Wani, 1995). Taxol has also shown promise in the treatment of breast and lung cancers (Wall & Wani, 1995). The most common application of plant-derived medicines in current orthodox medicine, is isolation of the key active constituent from the botanical source, establishing its chemistry, and ultimately attempting synthetic production of the compound. Paclitaxel, for example, is currently produced semi-synthetically via a precursor molecule extracted from the needles and twigs harvested from the yew tree. In the future, paclitaxel may be produced from cell culture using a *Taxus* species (Anon, 1996b). The use of whole plant extracts in orthodox medicine is currently very rare, because of the many difficulties involved in ensuring consistently bioequivalent extracts.

Table 5.1 Examples of Plant-Derived Constituents Used in Orthodox Medicine

Constituent (Type)	Botanical Source	Action/Clinical Use
Artemisiin (sesquiterpene)	Qinghao (*Artemisia annua*)	Antimalarial
Cocaine (alkaloid)	Coca (*Erythroxylum coca, E.truxillense*)	Local anaesthetic
Codeine (alkaloid)	Poppy (*Papaver somniferum*).	Analgesic, antidiarrhoeal, cough suppressant
Digitoxin, digoxin (cardenolide)	Digitalis (*Digitalis purpurea*)	Cardiac stimulant
Diosgenin (saponin)	Yam (*Dioscorea* spp.)	Female contraceptive
Ephedrine (alkaloid)	Ephedra (*Ephedra* spp.)	β-adrenoreceptor agonist
Hyoscine (alkaloid)	Belladonna (*Atropa belladonna)*	Antispasmodic, anti-emetic, cycloplegic, mydriatic
Hyoscyamine (alkaloid)	Belladonna (*Atropa belladonna)*	Parasympatholytic
Morphine (alkaloid)	Poppy (*Papaver somniferum*).	Narcotic analgesic
Physostigmine (alkaloid)	Calabar (*Physostigma venenosum*)	Parasympathomimetic
Pilocarpine (alkaloid)	Jaborandi (*Pilocarpus* spp.)	Parasympathomimetic
Podophyllum resin (lignan)	Podophyllum (*Podophyllum pelatum*)	Cytotoxic
Quinine (alkaloid)	Cinchona (*Cinchona* spp.)	Antimalarial
Reserpine (alkaloid)	Rauwolfia (*Rauwolfia serpentina*)	Antihypertensive

Constituent (Type)	Botanical Source	Action/Clinical Use
Sennosides A+B (anthraquinone)	Senna (*Cassia senna*)	Laxative
Taxol (diterpene)	Pacific Yew Tree (*Taxus brevifolia*)	Cytotoxic
Tubocurarine (alkaloid)	Curare - extract from *Chondrodendron tomentosum* (Menispermaceae)	Muscle relaxant
Vinblastine (alkaloid)	Periwinkle (*Catharanthus roseus*)	Cytotoxic
Vincristine (alkaloid)	Periwinkle (*Catharanthus roseus*)	Cytotoxic

Although an extensive traditional use exists for many of the whole herbs (rather than plant-derived compounds) used medicinally in Europe, there is little scientific or medical documentation in respect of their active constituents, pharmacological actions or clinical efficacy. Examples of this group include avens, boneset, burdock, clivers, damiana, jamaica dogwood, parsley piert, pulsatilla and wild lettuce. For other herbs, documented phytochemical or animal data may support traditional uses, but evidence of human efficacy is limited. Relatively few herbs have been subjected to rigorous scientific study, with their pharmacological activities and active principles successfully investigated. Examples of herbs that have been subject to such study include chamomile, echinacea, feverfew, ginkgo, hawthorn, hops, saw palmetto, uva-ursi, and valerian.

A number of factors specific to herbs need to be considered when attempting scientific validation of efficacy.

Lack of Phytochemical Data The chemical constituents of a herb can provide a useful indication of its pharmacological properties. Certain constituent types are associated with specific pharmacological actions (see Table 5.2) and this is discussed further under Section 5.2.

In vivo and In vitro Relevance In terms of efficacy the relevance of *in vivo* or *in vitro* animal studies, often the only information available, is questionable for any pharmacologically active substance.

Lack of Clinical Data Clinical trials require considerable resources, claimed to be far beyond the budget of many herbal remedy manufacturers. Of those studies performed, many are of inadequate trial design and therefore provide limited valid information. In addition, considerable variation in the nature of plant extracts used by different investigators makes comparison of trial results inappropriate. Hopefully the recent acquisition of phytomedicine companies by a number of multinational pharmaceutical companies (Table 5.2) will provide the additional resource and expertise required to undertake high quality clinical trials.

Formulated Product versus Crude Extract A formulated product containing, for example, an aqueous plant extract, equivalent to the same weight of a crude aqueous plant extract may not necessarily be bioequivalent. Most pharmacological studies *in vivo* involve the administration of a crude plant extract and not a formulated product. Many herbal remedies contain milligram doses of herbal ingredients which would appear sub-therapeutic when compared to therapeutic doses recommended in various herbal pharmacopoeias.

Table 5.2 Acquisitions of Botanical Companies by Multinational Pharmaceutical Companies[1]

Multinational Pharmaceutical Company	**Phytomedicine Company**
American Home Products	Dr. Much (Germany)

Multinational Pharmaceutical Company	Phytomedicine Company
Boehringer Ingelheim	Pharmaton (Switzerland) Quest (Canada)
Boots	Kanold (Germany)
Bausch & Lomb	Dr. Mann (Germany)
Degussa	Asta Medica (Germany)
Fujisawa	Klinge (Germany)
Johnson & Johnson / Merck	Woelm Pharma (Germany)
Pfizer	Mack (Germany)
Rhone-Poulenc Rohrer	Nattermann (Germany)
Sanofi	Plantorgan (Germany)
Searle	Heumann (Germany)
Smithkline Beecham	Fink (Germany)
Solvay	Kalichemis

[1] Anon, 1996f

5.2 Herbal Ingredients with Pharmacologically Significant Constituents

Plant secondary metabolites provide a wealth of structurally diverse compounds, the pharmacological activity of which is well recognised for many. Table 5.1 lists examples of plant constituents used in orthodox medicine. In addition there are many other plant constituents with pharmacologically significant actions that are present as constituents of herbs commonly used in European herbal remedies (Table 5.3). This Section will consider the major categories of pharmacologically significant plant constituents, their known pharmacological actions, and some examples of herbal ingredients containing these compounds.

Table 5.3 Pharmacologically Significant Constituents in Herbal Remedies

Constituent Type	Pharmacological Effect	Example of Herbal Source
Alkaloids		
Indole	CNS stimulant via MAO inhibition	Passionflower
Isoquinoline	Antibacterial, anti-inflammatory	Bloodroot, Golden Seal, Prickly Ash (Northern & Southern)
Piperidine	Nicotine-like action	Lobelia
Quinolizidine	Cardioactive	Broom
Xanthine	CNS stimulant	Cola, Mate
Essential Oil, Resins & Terpenes		
Monoterpenes	Antiseptic, carminative, diuretic, spasmolytic; irritant phenols/ ketones; sedative	Clove, Lime Flower, Peppermint, Rosemary, Sage, Valerian
Sesquiterpenes	Anti-inflammatory, anti-ulcerogenic	Feverfew, German Chamomile, Yarrow,
	Inhibition of platelet aggregation, and of prostaglandin, thromboxane and leukotrine production	Elecampane, feverfew
	Antibacterial, anti-inflammatory, anti-tumour	Holy Thistle
Sulphur-Containing Compounds	Antibacterial, antithrombotic, hypolipidaemic	Garlic

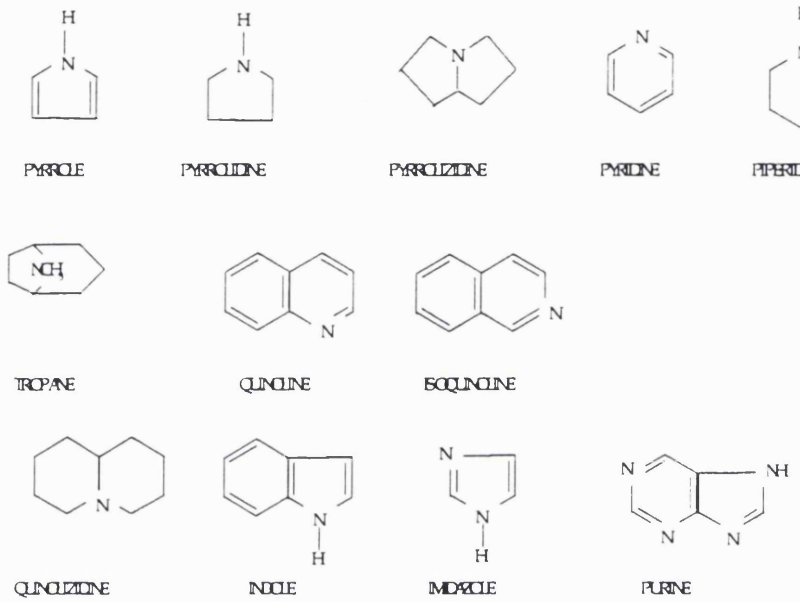
Constituent Type	Pharmacological Effect	Example of Herbal Source
Alkenylbenzene Derivatives	Psychoactive, sympathomimetic	Nutmeg, Aniseed
Iridoids	Anti-inflammatory, cardioactive	Devil's Claw, Figwort
	Bitter	Bogbean, Centaury, Gentian
	Laxative (slight)	Vervain
	Sedative	Valerian
Phenols		
Anthraquinones	Laxative	Aloes, Cascara, Frangula, Rhubarb, Senna, Yellow Dock
Coumarins	Anticoagulant	Alfalfa, Angelica, Aniseed, Asafoetida, Horsechestnut, Prickly Ash, Red Clover
Flavonoids	Anti-inflammatory, diuretic, oestrogenic, spasmolytic	Alfalfa, Cowslip, Fenugreek, German chamomile, Hawthorn, Liquorice, Red Clover, St. John's Wort, Yarrow
Simple Phenols	Antibacterial	Damiana, Uva-ursi
	Analgesic, anti-inflammatory, anti-pyretic	Meadowsweet, Poplar, Willow
	Irritant	Capsicum
Tannins	Astringent	Agrimony, Bayberry, Couchgrass, Eyebright, Uva-ursi, Witchazel
Saponins		
Pentacyclic	Anti-inflammatory, wound healing	Horsechestnut, Hydrocotyle, Liquorice, Senega
Steroidal	Hypocholesterolaemic, corticosteroidal, hormonal	Fenugreek, Ginseng, Sarsaparilla, Yucca

Constituent Type	Pharmacological Effect	Example of Herbal Source
Phytosteroids		
Cardenolides	Cardioactive	Pleurisy Root, Squill
Phytosterols	Oestrogenic	Alfalfa, Saw Palmetto
Carbohydrates	Demulcent, emollient	Aloe vera, Marshmallow, Slippery Elm
	Immunostimulant	Arnica, Echinacea, German Chamomile

5.2.1 Alkaloids

Alkaloids were the first chemical type of active constituent isolated from plants (Phillipson & Anderson, 1984a). Although there is no clear cut boundary between complex amines and alkaloids, an alkaloid can be defined as a naturally-occurring plant-derived basic substance containing one or more nitrogen atoms, usually in a heterocyclic ring system, that usually exerts a marked physiological action on man or other animals (Evans, 1996). Alkaloids can be classified on a pharmacological, biochemical or structural basis. The biochemical system classifies compounds according to the amino acid from which they are metabolically derived, i.e. ornithine (e.g. hyoscine, hyoscyamine), lysine (e.g. lobeline), phenylalanine (e.g. ephedrine, codeine, morphine) and tryptophan (e.g. ergotamine, quinine, reserpine, strychnine, vinblastine, vincristine). A small miscellaneous group represents alkaloids whose biosynthesis is either not established or is unrelated to an amino acid. The structural-based system classifies alkaloids according to their ring structure, sub-divided between non-heterocyclic (atypical) and heterocyclic structures. Figure 5.1 shows classification groups used for heterocyclic alkaloids.

Figure 5.1 Classification Groups of Heterocyclic Alkaloids



Alkaloids exhibit a variety of potent pharmacological actions, highlighted by the many alkaloids listed in Table 5.1. Activities associated with plant-derived alkaloid drugs include anaesthetic (cocaine), analgesic (codeine, morphine), antispasmodic (hyoscine), hypotensive (reserpine), antimalarial (quinine), cytotoxic (vinblastine, vincristine), muscle relaxant (tubocurarine), and ophthalmic (pilocarpine). At a molecular level alkaloids have been shown to affect subcellular structures (e.g. membrane disruption) and membrane transport processes (e.g. Na^+, K^+, and Ca^{2+} transport, amine re-uptake), and to act at neuroreceptors (e.g. cholinergic, adrenergic, opiate, serotonergic, purine and amino acid) (Robinson, 1986). It is reasonable to assume that any herb containing alkaloid constituents will exert some form of pharmacological action. Whether or not this action is observed depends on the level of alkaloid present in the herb, the dose of herbal ingredient, and on the presence of other constituents which may affect alkaloid-associated actions.

Of the 141 herbs considered by Newall et al (1996), some 46 contain alkaloid or amine constituents. For some of these 46 herbs, the alkaloid or amine compounds clearly represent their key pharmacologically active components. Goldenseal contains the isoquinoline alkaloids hydrastine and berberine, which are reported to have similar properties. Activities documented for berberine include antibiotic, immunostimulant, anticonvulsant, sedative, hypotensive, uterotonic, choleretic and carminative (Newall et al, 1996; Pizzorno & Murray, 1985). Bloodroot and prickly ash (Northern and Southern) contain isoquinoline alkaloids (benzophenanthridines), such as chelerythrine, nitidine, and sanguinarine. Activities documented for this class of alkaloids include antimicrobial, anti-inflammatory, anti-tumour, hypotensive and spasmolytic (Preininger 1975; Simanek 1985). The reported efficacy of bloodroot extracts in oral hygiene preparations such as oral rinses and toothpastes is attributable to the alkaloid constituents, primarily sanguinarine (Newall et al, 1996). Broom contains sparteine, an alkaloid with cardiac depressant actions similar to those of quinidine (Newall et al, 1996). Lobeline exhibits pharmacological actions similar to those of nicotine, and is the major alkaloid constituent of lobelia (Newall et al, 1996). The harman alkaloid constituents of passionflower are generally known to exert a central stimulant action via monoamine oxidase inhibition (Newall et al, 1996). However, it has been suggested that this stimulant effect may be masked by the sedative action of other constituents in passionflower (Newall et al, 1996). Various actions have been documented for protopine, the major alkaloid constituent in fumitory, including antihistaminic, hypotensive, bradycardic and sedative (small doses), stimulant and convulsive (high doses) (Preininger, 1975). The choleretic activity of boldo has been attributed to its alkaloid constituents (Newall et al, 1996). Boldine, the major alkaloid in boldo, is reported to increase hepatic and salivary gland secretions, as well as exhibiting mild sedative, diuretic and antiparasitic actions (Shamma, 1972). The pharmacological properties of the xanthine alkaloids (e.g. caffeine, theobromine) are well recognised and include stimulation of the CNS, respiratory system and skeletal muscle, cardiac stimulation, coronary dilatation, smooth muscle relaxation, and diuresis (Leung, 1980). Xanthines represent the active principles in cola and mate.

5.2.2 Essential Oils, Resins and Terpenes

The essential oil fraction of a plant may contain various classes of pharmacologically active constituents. Most commonly, pharmacological properties are associated with the terpene components such as mono-, sesqui- and diterpenes. Oxygenated terpenes (terpenoids) and another main component type, alkenylbenzene derivatives, are also associated with the toxicological effects of essential oils, and this is discussed in Chapter 4 under section 4.2.5. Other less common components, such as sulphur containing compounds, may be responsible for pharmacological activities associated with an essential oil (e.g. garlic). Diterpenes are commonly found in the resin fraction of plants.

5.2.2.1 Monoterpenes and Sesquiterpenes

Table 5.4 lists the main pharmacological actions documented for monoterpenes, sesquiterpenes, and diterpenes (Sticher, 1977). Activities ascribed to terpene components of essential oils include antibiotic, anti-inflammatory, antirheumatic, diuretic, expectorant, hypotensive, irritant, purgative, sedative and spasmolytic (Sticher, 1977). In view of these known actions, the reputed actions and uses of many herbal remedies can be associated with their essential oil fraction. Indeed for some herbs, pharmacological studies have identified activities attributable to the essential oil.

Table 5.4 Examples of Pharmacological Properties Documented for Mono-, Sesqui- and Diterpenes[1]

Activity	Monoterpenes	Sesquiterpenes	Diterpenes
Anaesthetic	+		
Anthelmintic	+		
Antiarrhythmic	+	+	
Antibiotic	+	+	+
Antiepileptic		+	
Antihistaminic	+		
Anti-inflammatory, antiphlogistic	+	+	
Antirheumatic, anti-arthritic	+		
Antitumour	+	+	+
Choleretic, cholagogue		+	
Diuretic	+		
Expectorant	+		+
Hypotensive	+	+	+
Insecticidal	+		+
Irritant	+	+	
Purgative	+		+
Sedative	+	+	
Spasmolytic	+	+	

[1] adapted from Sticher, 1977

Antimicrobial The antimicrobial activity of many herbs has been associated with their volatile oil or oleo-resin constituents. Clove oil, for example, has anodyne and

antiseptic properties that have been attributed to eugenol. Antibacterial properties have been reported for eucalyptus oil and specifically for the main component, cineole. Activity has been reported against both Gram-positive and Gram-negative organisms (Kumar et al, 1988). Antimicrobial activity towards moulds, and Gram-negative and Gram-positive bacteria has been reported for rosemary oil (Collin & Charles, 1987; Opdyke, 1974c). The antimicrobial activity of sage oil has been ascribed to thujone (Jalsenjak et al, 1987), with activity noted against fungi, Gram-negative and Gram-positive bacteria (Recio et al, 1989). The anthelmintic properties of some oils are generally attributable to toxic components of the oil, such as β-thujone in tansy oil and ascaridole in wormseed oil. The toxicity of these compounds precludes from their clinical usefulness. Sesquiterpene lactone components of elecampane oil are reported to exhibit high bactericidal and fungicidal properties *in vitro* (Leung, 1980) The antibacterial activity of hops, mainly towards Gram-positive bacteria, has been credited to oleo-resin components (bitter acids) (Teuber & Schmalreck, 1973).

Anti-inflammatory The anti-inflammatory activity documented for german chamomile has been partly associated with sesquiterpene components of the essential oil, in particular to (-)-α-bisabolol (Jakovlev et al, 1979; Mann & Staba, 1986). Anti-ulcerogenic activity in rats has also been reported for (-)-α-bisabolol, when tested against indomethacin, stress, and ethanol inducers (Mann & Staba, 1986; Szelenyi et al, 1979). The anti-inflammatory properties of azulene (sesquiterpene lactone-derived artefacts formed during steam distillation) compounds (e.g. chamazulene) are well known (Sticher, 1977) and are thought to contribute to the anti-inflammatory activity exhibited by german chamomile and yarrow. Sesquiterpene constituents, in particular parthenolide, are considered to be the active principles in feverfew, which has been documented to inhibit platelet aggregation, granule secretion in platelets and neutrophils, and prostaglandin, thromboxane, and leukotriene production (Capasso, 1986; Collier et al, 1980; Heptinstall et al, 1985; Makheja & Bailey, 1982). Ginger oleo-resin components (gingerols) have been reported to be potent inhibitors of prostaglandin biosynthesis *in-vitro*, with some compounds more potent than indomethacin (Kiuchi et al, 1982). Indeed, fresh or powdered ginger has been reported to elicit a beneficial response (reduction in joint pain, increase in joint movement) in

rheumatoid arthritis sufferers, with a dual inhibition of cyclo-oxygenase and lipoxygenase pathways suggested as a mechanism of action (Srivastava, 1989; Srivastava & Mustafa, 1989).

Irritant, Diuretic, Expectorant Many oxygenated terpenes (terpenoids) possess irritant properties (Tisserand & Balacs, 1995). Certain essential oils may be applied externally as counter-irritants in the form of embrocations or liniments. They produce an initial feeling of warmth and smarting which is often followed by a mild local anaesthesia. Common ingredients of external preparations for rheumatic pains and strains include camphor, menthol, salicylates, eucalyptus oil, and turpentine oil (Anon, 1996a). Inhalation preparations often contain irritant oils, such as eucalyptus, to act as mild expectorants and cough stimulants via an irritant action on the bronchial tissue (Sticher, 1977). The more water-soluble essential oil constituents, such as terpenoid alcohols, aldehydes and esters, are thought to be excreted via the kidney (Tisserand & Balacs, 1995). The diuretic properties associated with many essential oils are therefore probably attributable to the action of irritant components during renal excretion. The diuretic action documented for buchu, boldo, juniper, and yarrow for instance, is most likely attributable to the irritant terpenoid components in the volatile oil.

Sedative A sedative effect (central nervous depression) has been reported for a number of monoterpenes and sesquiterpenes, and for essential oils including asafoetida, calamus, elecampane, german chamomile, lavender, marjoram, melissa, nutmeg, valerian and yarrow (Reiter & Brandt, 1985; Tisserand & Balacs, 1995). The sedative properties of valerian have been extensively investigated in both animals and humans, with activity attributed to the essential oil, iridoid components (valepotriates), and possibly to an additional unknown constituent. Valerenic acid, a key sedative component of valerian essential oil, has been reported to exhibit a central nervous system (CNS) depressant effect in mice similar to that of pentobarbitone (Hendriks et al, 1985).

Spasmolytic A spasmolytic action on both smooth and cardiac muscle has been documented for a number of essential oils, and for monoterpene and sesquiterpene

components (Reiter & Brandt, 1985), and has been reviewed by Tisserand & Balacs (1995). The spasmolytic action of essential oils has been linked with antagonism of acetylcholine in smooth muscle (Reiter & Brandt, 1985) and with inhibition of calcium ion flow in cardiac and vascular muscle. An inhibition of calcium ion channels has been reported for bisabolol, eugenol, δ-carvone, δ-menthol and possibly for trans-anethole. A depressant effect on the myocardium has been documented for peppermint and rosemary oils and has been linked to their effect on calcium ion flow. Interestingly, bradycardia has been reported in a person addicted to menthol cigarettes. Essential oil constituents that exhibit a hypotensive action, probably attributable to vasodilation, include cineole, citronellol, geraniol, linalool, nerol, and terpineol. Hypotensive essential oils include carrot, garlic, geranium, hyssop, lavender, peppermint and rosemary (Tisserand & Balacs, 1995).

Essential oils may contain spasmogenic and spasmolytic components, their relative concentration affecting the overall pharmacological action observed. The spasmolytic action of rosemary oil, for example, is preceded by a contractile action attributable to the α- and β-pinene components of the oil (Taddei et al, 1988). Similarly, an initial spasmogenic action of sage oil have been attributed to pinene constituents. α- and β-pinenes are known to elicit a spasmogenic action towards smooth muscle, with no effect on cardiac muscle (Hof & Ammon, 1989). The spasmolytic actions of peppermint and rosemary oils have been primarily attributed to menthol and borneol, respectively. Elecampane oil, in which sesquiterpene lactone components predominate, has been reported to exert a potent smooth muscle relaxant effect *in vitro* (Reiter & Brandt, 1985).

Two licensed medicines containing peppermint oil (Colpermin, Mintec) are available in the UK and are indicated for the treatment of symptoms of discomfort, pain and distension associated with irritable bowel or spastic colon syndrome (Anon, 1995c). The carminative action of essential oils has been linked with their spasmolytic effect (Sticher, 1977).

5.2.2.2 Sulphur-Containing Compounds

Numerous pharmacological activities have been documented for garlic and are associated with the odiferous sulphur components of the essential oil, notably allicin and its degradation products. Pharmacological properties documented for garlic include antimicrobial (antibacterial, antifungal, antiviral) and cardiovascular effects such as hypolipidaemic and antithrombotic actions (Newall et al, 1996).

5.2.2.3 Alkenylbenzene Derivatives

The psychoactive actions documented for nutmeg have been attributed to the essential oil constituents myristicin and elemicin. It has been reported that both compounds may potentially be metabolised to known hallucinogenic compounds (Tisserand & Balacs, 1995). In addition, myristicin reportedly inhibits elimination of the neurotransmitter monoamine oxidase, which may also account for its euphoric effects (Tisserand & Balacs, 1995). Other components of nutmeg oil are thought to act synergistically with myristicin and elemicin, since myristicin ingested alone is reportedly devoid of psychoactive effects (Tisserand & Balacs, 1995). A weak oestrogenic action has been documented for anethole, and it is advised that anethole-rich oils (anise, fennel, star anise) should be used with caution orally in people with oestrogen-dependent cancers, and in endometriosis, pregnancy and breastfeeding. Interestingly, anethole dimers closely resemble oestrogenic agents stilbene and stilboestrol (Albert-Puleo, 1980). The pharmacological actions of aniseed are largely due to anethole, which is structurally similar to the catecholamines adrenaline, noradrenaline and dopamine. Sympathomimetic effects of aniseed in humans have been attributed to anethole (Albert-Puleo, 1980). In addition, a lactogogic action has also been attributed to anethole which exerts a competitive antagonism at dopamine receptor sites (dopamine inhibits prolactin secretion), and to the action of anethole dimers (Albert-Puleo, 1980).

5.2.2.4 Iridoids

Iridoids are monoterpenoid compounds whose structure also involves a pyran ring. A number of plants used in European herbal remedies contain iridoid constituents which have been associated with a variety of pharmacological properties. Bogbean (*Menyanthes trifoliata*), centaury (*Centaurium erythraea*) and gentian (*Gentiana lutea*) all possess bitter properties that are attributable to their iridoid constituents (Newall et al, 1996). A stimulant laxative action, weaker than senna, has been documented for various iridoid glycosides including aucubin. Anti-inflammatory and cardioactive actions documented for devil's claw (*Harpagophytum procumbens*) have been attributed to the iridoid constituents, especially harpagide and harpagoside. Numerous studies have investigated the sedative actions of valerian (*Valeriana officinalis*). Iridoid constituents (valepotriates) are thought to be one of the active constituent fractions, together with the volatile oil and possibly some other, as yet unidentified, constituent. However, the valepotriates are known to be highly unstable in both acidic and alkaline media and therefore probably degrade when taken orally (Newall et al, 1996).

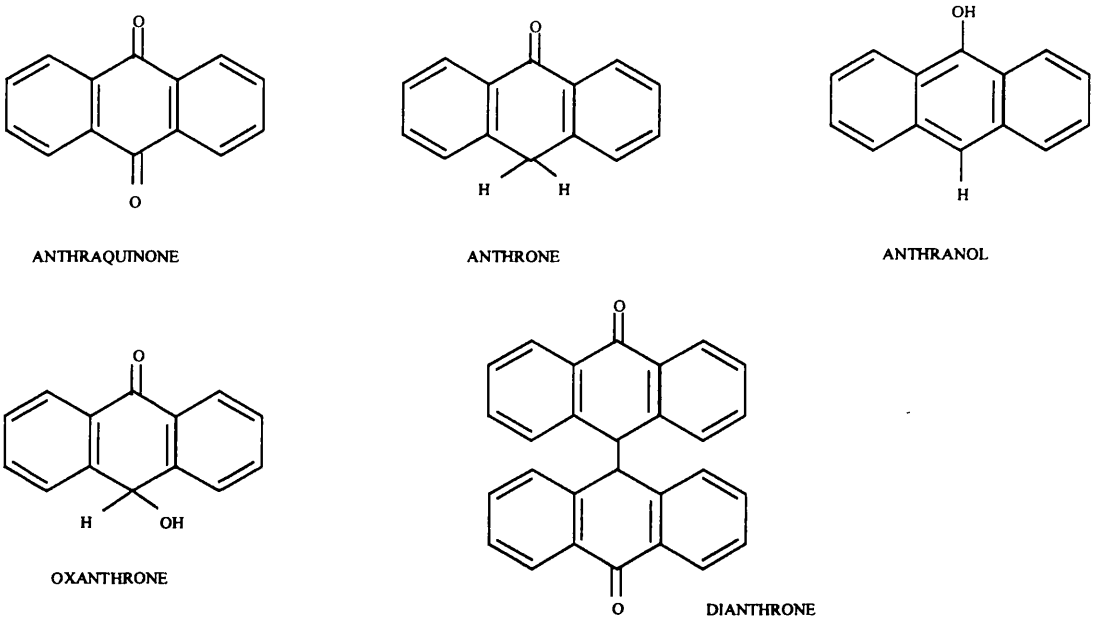
5.2.3 Phenols

5.2.3.1 Anthraquinones

The stimulant laxative effect of anthraquinone glycosides is well recognised, and many plants containing these constituents are used in proprietary laxative medicines. Anthraquinone glycosides are carried to the colon where, following bacterial hydrolysis, the aglycones exert a direct laxative effect (Reynolds, 1996). Anthraquinone-containing plants that are traditionally used for their laxative action include senna, rhubarb, cascara, frangula, aloes and yellow dock. The anthraquinone glycoside constituents of herbal laxatives are based on either the anthraquinone nucleus, on reduced derivatives (anthrone, anthranol, oxanthrone), or on a dimer consisting of two anthrone molecules (dianthrone) (Figure 5.2) (Evans, 1996). The anthraquinone aglycones of the many anthraquinone glycoside herbal laxatives have long been established and include chrysophanol from rhubarb and cascara, aloe-emodin from

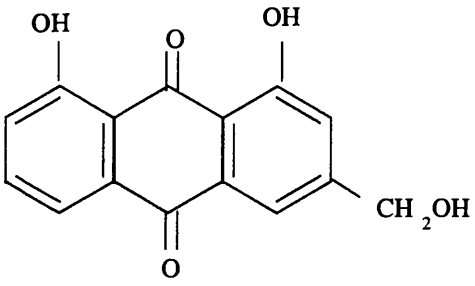
rhubarb and senna, rhein from rhubarb and senna, and emodin from rhubarb and cascara) (Evans, 1996).

Figure 5.2 Anthraquinone-Derived Structures

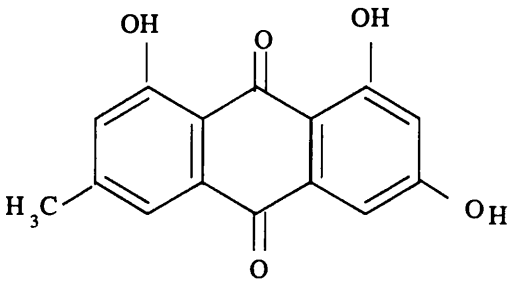


Antiviral activity against HIV and hepatitis C has been documented for hypericin, an anthraquinone derivative constituent of St. John's Wort (Anon, 1989b; Anon, 1995a&b), although the mechanism of action is unclear (Hudson et al, 1994).

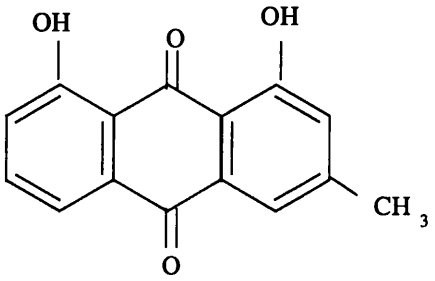
Figure 5.3 Examples of Anthraquinone Aglycones



ALOE-EMODIN



EMODIN

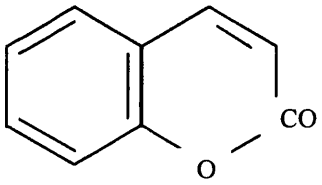


CHRYSOPHANOL

5.2.3.2 Coumarins

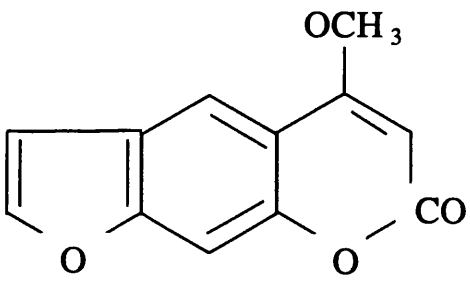
Coumarins are phenylpropane derivatives (Figure 5.4) which occur in numerous plant species as either aglycones or as glycosides. Biological activities documented for coumarins include anticoagulant, diuretic, photosensitivity, molluscocidal, oestrogenic, hypnotic, antispasmodic, rodenticidal, antiatherosclerotic and vasodilatory (Schwarting, 1977). Anticoagulant activity requires an intact 4-hydroxycoumarin nucleus with a carbon constituent at the 3-position (DeSmet et al, 1992). The clinical significance of coumarin-containing herbs is therefore dependent on the chemical structure of the coumarin derivatives.

Figure 5.4 Coumarin



Coumarins have been identified as active constituents in a number of herbs including alfalfa, angelica, aniseed, asafoetida, horsechestnut, prickly ash, and red clover. The clinical significance of the coumarin constituents in these herbs is unclear because an anticoagulant action is rarely mentioned in results of pharmacological studies. Of probable greater relevance is the potential for interactions with existing medicines or clinical conditions, especially when coumarin-containing herbs are taken in excess.

Figure 5.5 Furanocoumarin e.g. Bergapten



Furanocoumarins (Figure 5.5) occur in species of Rutaceae and Umbellifereae. Furanocoumarins elicit a photosensitising action on the skin and are discussed in Chapter 4 under Sections 4.2.6 and 4.3.3.

5.2.3.3 Flavonoids

The flavonoids occur both as glycosides and in the free state, and are the largest group of naturally occurring phenols (Evans, 1996). Flavonoids are based on the benzopyrone molecule and classifications can be made depending on the various derivative structures into flavone, isoflavone, flavonol, flavanone, xanthone and chalcone (Figure 5.6) (Evans, 1996). Some common flavonoid aglycones are shown in Figure 5.7. Flavonoids have been associated with a variety of pharmacological actions including anti-inflammatory, anti-histamine, antioxidant, antimicrobial, central vascular effects (e.g. anti-arrhythmic, antihypertensive, capillary strengthening, hypolipidaemic, antiplatelet aggregation and secretion, spasmolytic), oestrogenic, antihepatotoxic and antitumour (McClure, 1975; Middleton, 1988; Pathak et al, 1991). In general, biflavonoids have been reported to be more active than their monomeric counterparts (Geiger & Quinn, 1982). Oestrogenic properties are primarily associated with isoflavonoids such as coumestrol, formononetin and genistein, although weak activity has been reported for flavonol (quercetin, kaempferol) derivatives (McClure, 1975).

Figure 5.6 **Flavonoid Structural Types**

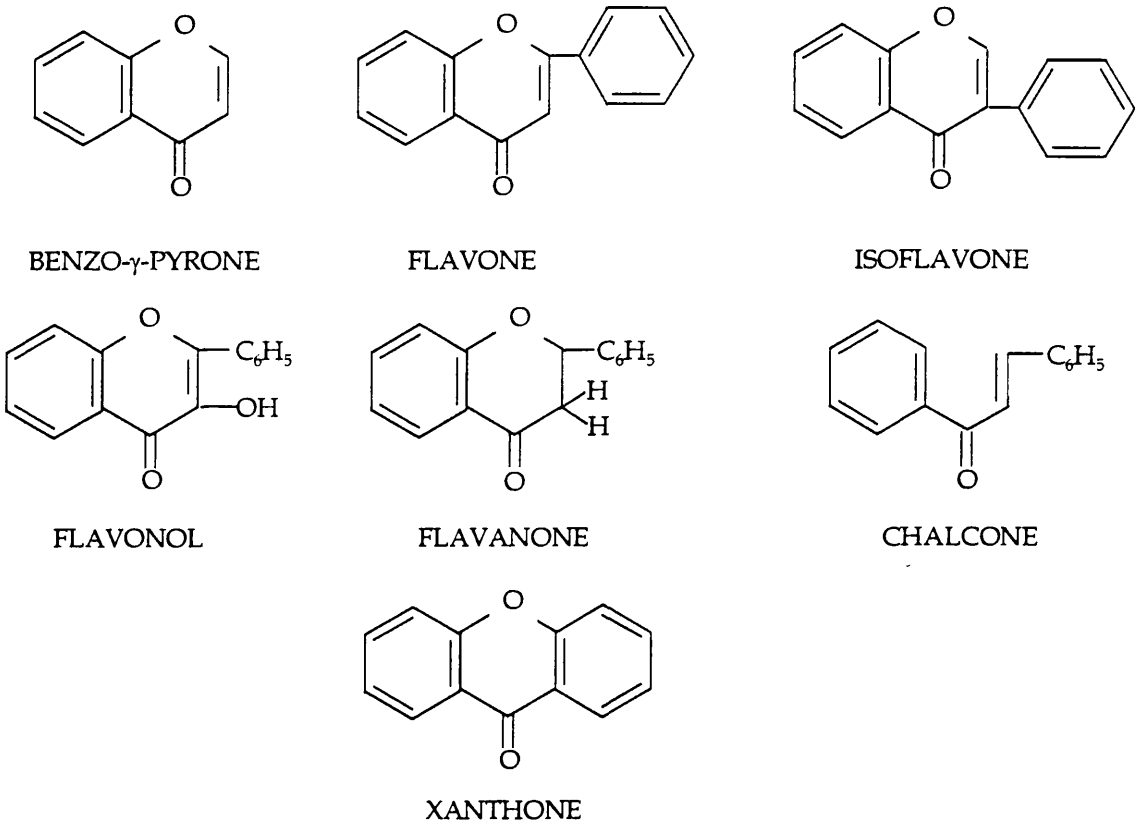
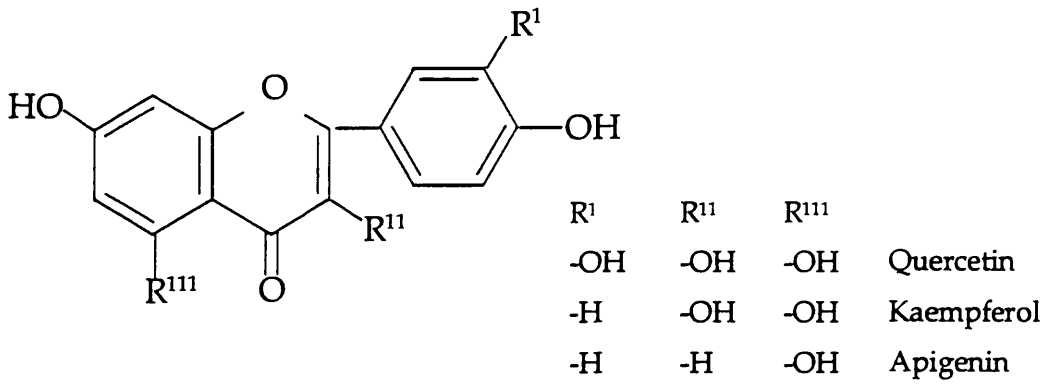


Figure 5.7 **Examples of Common Flavonoid Aglycones**



R^1	R^{11}	R^{111}	
-OH	-OH	-OH	Quercetin
-H	-OH	-OH	Kaempferol
-H	-H	-OH	Apigenin

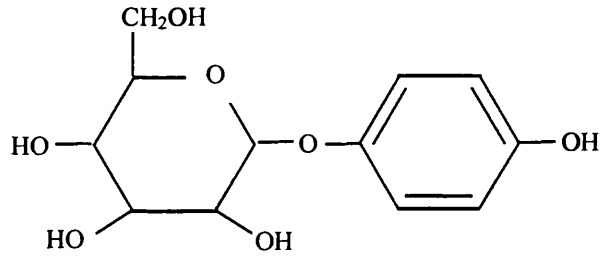
Flavonoids are common constituents of many herbal remedies, including alfalfa, cowslip, fenugreek, german chamomile, hawthorn, liquorice, red clover, St. John's wort

and yarrow. The oestrogenic activity documented for alfalfa, liquorice and red clover can be attributed to their isoflavonoid constituents (Newall et al, 1996). Many flavonoid-containing herbs are reported to exhibit anti-inflammatory, anti-microbial and spasmolytic actions. In many cases these actions can be attributed to more than one constituent-type. For example the anti-inflammatory and spasmolytic actions of german chamomile and yarrow are probably associated with the essential oil and flavonoid constituents; the anti-inflammatory actions of feverfew have been associated with the sesquiterpene lactone constituents and, more recently a flavonol component (Newall et al, 1996; Williams et al, 1995). The sedative action documented for St. John's wort may be attributable to the biflavonoid constituents (Berghofer & Holzl, 1987). The many cardiovascular actions documented for hawthorn are associated with its flavonoid constituents. Hawthorn extracts have been reported to increase coronary blood flow, reduce blood pressure (attributed to a vasodilatory effect), exert negative chronotropic, positive inotropic and anti-arrhythmic effects (Abdul-Ghani et al, 1987; Ammon & Handel, 1981a,b,c; Leukel et al, 1986; Lievre et al, 1985; Petkov, 1979; Racz-Kotilla et al, 1980; Thompson et al, 1974)

5.2.3.4 Simple Phenols

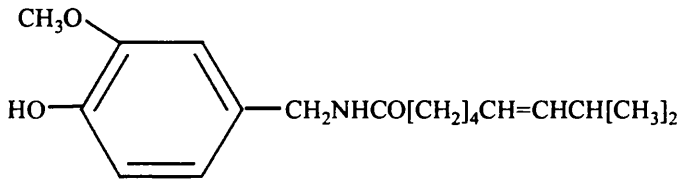
Arbutin Arbutin (Figure 5.8) is the principle antibacterial constituent in uva-ursi, which has traditionally been used as a urinary antiseptic (Newall et al, 1996). In alkaline conditions, arbutin yields hydroquinone, the active aglycone. The antibacterial activity of arbutin towards bacteria implicated in producing urinary tract infections, has been found to be directly dependent on the β-glucosidase activity of the infective organism (Jahodar et al, 1985). Highest enzymatic activity, and therefore susceptibility to arbutin, was shown by *Enterobacter*, *Klebsiella*, and *Streptococcus* genera, and lowest by *Escherichia coli* (Jahodar et al, 1985).

Figure 5.8 Arbutin



Capsaicin The capsaicinoids are the pungent principles in *Capsicum* species (chillis) and are principally responsible for the biological activities of capsicum. Capsaicin (Figure 5.9) is the major capsaicinoid in capsicum (Newall et al, 1996). In addition to being highly irritant to mucous membranes, capsaicin has been used as a neurochemical tool for studying sensory neurotransmission. (Locock, 1985). The irritant properties of capsicum are utilised externally in many counter-irritant preparations used for rheumatism, arthritis, neuralgia, and lumbago.

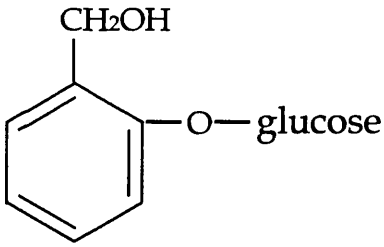
Figure 5.9 Capsaicin



Salicin Salicin (Figure 5.10) is the principle salicylate glycoside constituent of willow, which has traditionally been used in inflammatory conditions. The pharmacological actions of salicylates in man are well documented and include anti-

inflammatory, antipyretic, dose dependent hyperglycaemic/hypoglycaemic and uricosuric/antiuricosuric activities, increase in blood clotting time, and plasma-albumin binding (Anon, 1996a). Salicin is a prodrug which is metabolised to saligenin in the gastro-intestinal tract and to salicylic acid after absorption (Meier et al, 1988). Other salicylate-containing herbs include meadowsweet and poplar.

Figure 5.10 Salicin



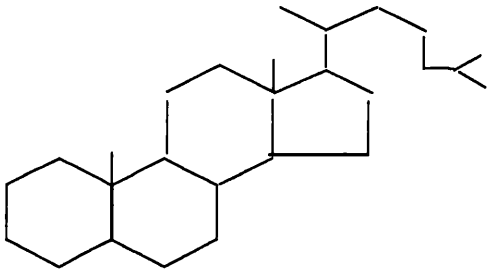
5.2.3.5 Tannins

Tannins are high molecular weight (range usually 1000-5000) phenolic compounds that are generally classified into two groups, hydrolysable and condensed. A third group, named pseudotannins, refers to lower molecular weight phenolic compounds that are often associated with true tannins, but which do not respond to a tanning test. Hydrolysable tannins may be hydrolysed by acid or enzymes and are formed from several molecules of phenolic acids such as gallic and ellagic acids. Condensed tannins (proanthocyanidins) include all other true tannins and are much more resistant to breakage than hydrolysable tannins (Evans, 1996). Properties and uses documented for tannins include effects on the vascular system, antiviral (antiherpetic) effect, microbial toxicity (antiseptic action), inhibition of direct acting mutagens, use in stomach disorders, dysentry, diarrhoea and haemorrhages, and use in wound management. The astringent action of many plants is attributable to their tannin constituents. Herbs containing tannins often have a traditional use in treating bruises, diarrhoea, and haemorrhoids. Witch hazel is probably one of the most well known tannin-containing plants, with extracts utilised for both medical and cosmetic purposes (Haslam, 1989).

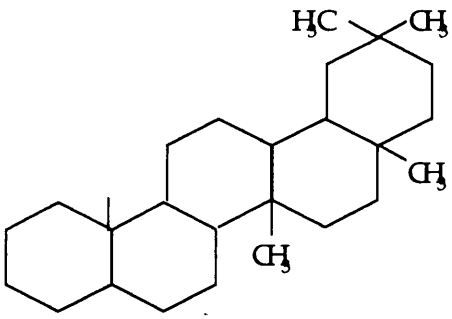
5.2.4 Saponins

Saponins are high molecular weight glycosides with aglycones referred to as sapogenins. Saponins are classified into two groups based on their sapogenin structure, namely pentacyclic triterpenoid or steroidal (tetracyclic triterpenoid) (Figure 5.11). Saponins are characterised by their ability to produce a frothing aqueous solution and by their haemolytic, cholesterol complexation and piscicidal properties, although exceptions do exist to these definitions (Evans, 1996; Hostettmann & Marston, 1995). Numerous additional pharmacological properties have been documented including antimicrobial, cytotoxic and antitumour, molluscicidal, spermicidal, insecticidal, anthelmintic, expectorant and antitussive, diuretic, hypolipidaemic, antiarrhythmic, vasodilatory, anti-inflammatory, capillary-strengthening, anti-ulcer, sedative, analgesic and adaptogenic (Hostettmann & Marston, 1995).

Figure 5.11 Pentacyclic and Steroidal Sapogenin Structures



STEROIDAL SAPOGENIN



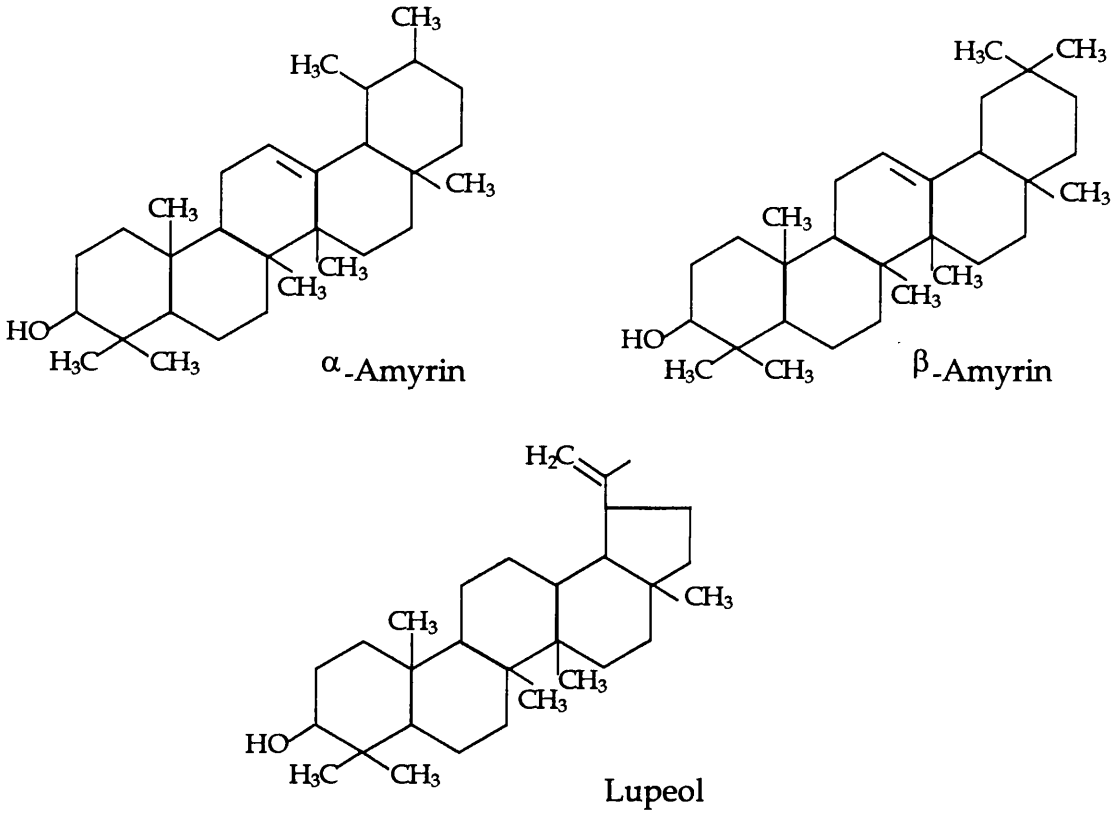
PENTACYCLIC SAPOGENIN

5.2.4.1 Pentacyclic Saponins

Pentacyclic saponins can be classified into three groups based on their sapogenin structure. The three structural types can be represented by α-amyrin, β-amyrin and

lupeol (Figure 5.12). Related triterpene acids, such as glycyrrhizic, oleanolic and ursolic, are formed by replacement of a methyl group by a carboxyl group in positions 4, 17 or 20 (Evans, 1996). Many plants used in herbal remedies contain pentacyclic saponins, including ginseng (see steroidal), horse-chestnut, hydrocotyle, liquorice and senega.

Figure 5.12 Pentacyclic Saponins



Horse-chestnut (*Aesculus hippocastanum*) contains a mixture of saponins collectively referred to as aescin. Activities attributed to the saponin constituents include anti-inflammatory, analgesic, antigranulation and a reduction in capillary permeability (Benoit et al, 1976; Cebo et al, 1976; De Pascale et al, 1974; Farnsworth & Cordell, 1976; Vogel et al, 1970). It has been proposed that aescin affects the initial phase of inflammation by exerting a "sealing" effect on capillaries and by reducing the number and/or diameter of capillary pores (Cebo et al, 1976). In addition, aescin has been reported to increase venous tone by increasing local production of prostaglandin $F_{2\alpha}$.

Prostaglandins of the E series are known to cause relaxation of venous tissue, whereas those of the Fα series produce contraction (Longiave et al, 1978). In humans horse-chestnut extracts have proved beneficial in patients with chronic venous insufficiency, demonstrating an anti-oedamatous effect (Bisler et al, 1986; Rudofsky et al, 1986).

Hydrocotyle (*Centella asiatica*) The triterpenoid saponins are considered to be the active principles in hydrocotyle, with wound healing, anti-inflammatory, ulcer protection and CNS depressant actions documented (Jacker et al, 1982; Morisset et al, 1987; Ramaswamy et al, 1970; Ravokatra & Ratsimamanga, 1974; Ravokatra et al, 1974). Several human studies describing the use of hydrocotyle to treat wounds and various skin disorders such as ulcers, leprosy and scleroderma have been documented (Anon, 1996a; Bosse et al, 1979; Kartnig, 1988; Morisset et al, 1987; Natarajan & Paily, 1973). Modes of action for the wound healing ability of the triterpenoids include epidermal stimulation and promotion of keratinisation, and interference with abnormal collagen metabolism (Bosse et al, 1979; Morisset et al, 1987).

The steroidal-type actions of the triterpene saponin constituents of liquorice (*Glycyrrhiza glabra*) are well documented. Glycyrrhizin is the main saponin yielding glycyrrhetinic acid as the aglycone. Both glycyrrhizin and glycyrrhetinic acid have been reported to bind to glucocorticoid and mineralocorticoid receptors with moderate affinity, and to oestrogen receptors, sex-hormone-binding globulin and corticosteroid-binding globulin with very weak affinity (Armanini et al, 1983; Armanini et al, 1985; Tamaya et al, 1986). It has been suggested that glycyrrhizin and glycyrrhetinic acid may influence endogenous steroid activity via a receptor mechanism, with displacement of corticosteroids or other endogenous steroids (Tamaya et al, 1986). However, the relatively low affinity of glycyrrhizin and glycyrrhetinic acid for binding to mineralocorticoid receptors together with the fact that liquorice does not exert its mineralocorticoid activity in adrenalectomised animals, indicates that a direct action at mineralocorticoid receptors is not the predominant mode of action (Stewart et al, 1987). It has been suggested that glycyrrhizin and glycyrrhetinic acid may exert their mineralocorticoid effect via an inhibition of 11β-hydroxysteroid, a microsomal enzyme complex found predominantly in the liver and kidneys which catalyses the conversion

of cortisol (potent mineralocorticoid activity) to the inactive cortisone (Stewart et al, 1987). Other actions documented in animals for glycyrrhetinic acid include anti-inflammatory, antiviral, and hepatoprotective activity (Amagaya et al, 1985; Fujita et al, 1980; Kiso et al, 1984; Pompei et al, 1980). In humans carbenoxolone, an ester derivative of glycyrrhetinic acid, has been used in the treatment of gastric and oesophageal ulcers. It is thought to exhibit a mucosal-protecting effect by beneficially interfering with gastric prostanoid synthesis, and increasing mucous production and mucous blood flow (Guslandi, 1985). The side-effects associated with excessive liquorice ingestion are discussed in Chapter 4 under Section 4.3.1.

5.2.4.2 Steroidal Saponins

These compounds are structurally similar to molecules such as sex hormones, corticosteroids, oral contraceptives, and diuretic steroids, and have been utilised as starting materials for the partial biosynthesis of medicinal steroids. Diosgenin, which is obtained from various *Dioscorea* (yam) species and from fenugreek, is used as a starting material for the manufacture of oral contraceptives and sex hormones (Evans, 1996). Steroidal saponins are constituents of a number of plants used in European herbal remedies, for example fenugreek, ginseng, sarsaparilla, and yucca.

Panax ginseng (various *Panax* species) contains both steroidal and pentacyclic saponin glycosides (ginsenosides), which are generally considered to be the main active constituents (Newall et al, 1996). Many of the pharmacological actions documented for ginseng directly oppose one another and this has been attributed to the actions of individual ginsenosides. For example, one ginsenoside may exhibit CNS-stimulant, hypertensive and anti-fatigue actions, whilst another exhibits CNS-depressant, hypotensive and tranquillising actions. These opposing actions are thought to explain the "adaptogenic" reputation of ginseng, that is the ability to increase the overall resistance of the body to stress and to balance bodily functions (Newall et al, 1996).

Anti-inflammatory exhibited by a yucca extract in rats was attributed to the saponin constituents (Bingham et al, 1975). In humans, a reduction in arthritic symptoms of

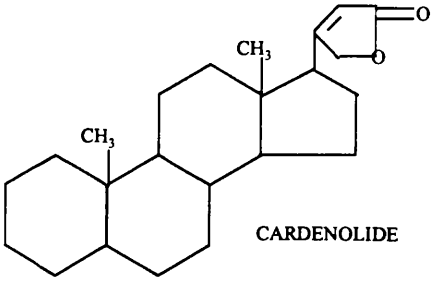
swelling, pain and stiffness has been reported for a saponin-containing yucca extract. Hypolipidaemic activity for fenugreek and yucca has been attributed to their saponin constituents (Bingham et al, 1978; Ribes et al, 1987; Sharma, 1986)

5.2.5 Phytosteroids

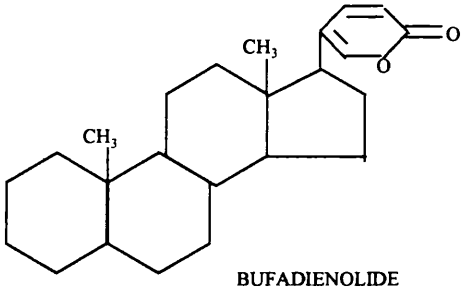
5.2.5.1 Cardenolides

Cardenolides are steroidal glycosides that exert a negative chronotropic and a positive inotropic action on the heart. Cardenolides can be classified into two structural types, namely cardenolide and bufadienolide (Figure 5.13) (Evans, 1996). The cardioactive properties of the genus *Digitalis* are well recognised and are attributable to the cardenolide constituents. Pleurisy root (*Asclepias tuberosa*) and squill (*Drimia maritima*) both contain cardiac glycoside constituents. Little phytochemical information has been documented for pleurisy root, although cardenolide glycosides have been reported for many *Asclepias* species including *A.tuberosa* (Conway & Slocumb, 1979; Jolad et al, 1986; Radford et al, 1986; Seiber et al, 1982; Seiber et al, 1985). Squill is commonly used in expectorant preparations and contains bufadienolide glycosides. The squill cardiac aglycones are poorly absorbed from the gastro-intestinal tract and are less potent than the digitalis glycosides (Anon, 1989a; Court, 1985). Excessive ingestion of squill is limited by the irritant nature of the saponins, which stimulate a vomiting reflex in large doses.

Figure 5.13 Cardenolide and Bufadienolide Structures



CARDENOLIDE

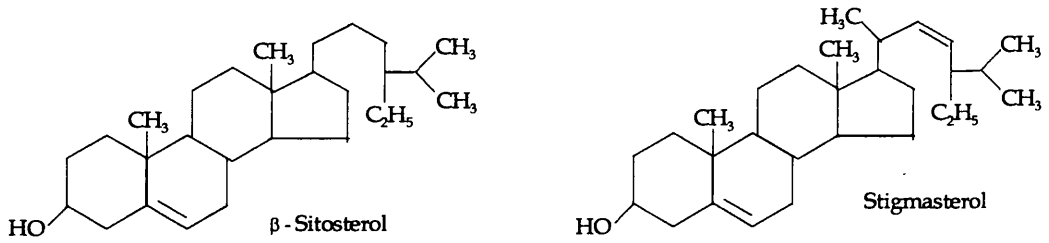


BUFADIENOLIDE

5.2.5.2 Phytosterols

Many plants contain non-sapogenin steroids, primarily sitosterol and stigmasterol (Figure 5.14). The soya bean contains appreciable quantities of phytosterols which are used extensively in the manufacture of steroids (Evans, 1996).

Figure 5.14 β-Sitosterol and Stigmasterol



5.2.6 Carbohydrates

High molecular weight polysaccharide (HMWP) constituents of some plants, such as arnica, german chamomile and echinacea have been investigated for their potential immunostimulant properties. It is thought that the HMWPs influence mainly unspecified cellular and/or humoral immune defence mechanisms. Immunostimulant activity has been assessed by various *in vitro* and *in vivo* test systems measuring the effect of extracts on granulocyte and macrophage phagocytosis, lymphocyte activity, and on the liberation of mediators such as interferon, prostaglandins and lymphokines (Wagner, 1987).

Some plants, such as aloe vera, marshmallow and slippery elm, have a high mucilage content and are therefore utilised as emollients and demulcents.

5.3 Examples of Herbal Medicines of Current Interest

There is an increasing number of herbs for whom a considerable amount of clinical research has been documented (Table 5.5). Some of these herbs are considered below.

Table 5.5 Examples of Herbal Remedies of Current Interest

Herbal Ingredient	Pharmacological /Therapeutic Action	Suggested Active Principle
Agnus castus	Hormonal; action on pituitary-hypothalamic axis; beneficial effect in menstrual disorders	Unknown
Echinacea	Immunostimulant	High molecular weight polysaccharides
Evening Primrose	Beneficial effect in disorders associated with low levels of gamolenic acid, e.g. atopic eczema, mastalgia	Fatty acids in oil, especially linolenic and gamolenic acid
Feverfew	Migraine prophylaxis	Sesquiterpene lactones
Ginger	Anti-emetic in motion sickness	Gingerols (oleo-resin components)
Ginkgo	Anti-PAF; beneficial effect in cerebral and peripheral arterial insufficiency	Ginkgolides (diterpenes)
Ginseng	Many actions including cardiovascular and hormonal	Ginsenosides (triterpenoid saponins); eleutherosides (heterogenous mixture)
Saw Palmetto	Anti-androgenic; beneficial in benign prostatic hypertrophy	? Sterols

Herbal Ingredient	Pharmacological /Therapeutic Action	Suggested Active Principle
St. John's Wort	Antidepressant Antiviral	? Flavonoids, hypericin (anthraquinone derivative) Hypericin
Valerian	Sedative	Essential oil, valepotriates (iridoids)

5.3.1 Agnus Castus (*Vitex agnus castus*)

Agnus castus (*Vitex agnus-castus*) is a small shrub indigenous to the Mediterranean countries and Asia. The fruit has traditionally been used for menstrual problems resulting from corpus luteum deficiency, including premenstrual symptoms and spasmodic dysmenorrhoea, for certain menopausal conditions, and for insufficient lactation (Mills, 1985). A proprietary preparation containing an alcoholic extract of agnus castus (0.2%w/w) has been available in Germany since the 1950's. It has been used in the treatment of breast disease and pain, ovarian insufficiency, and dysfunctional uterine bleeding (Amann, 1979a&b; Amann, 1982; Houghton, 1994d; Turner & Mills, 1993). Numerous studies have been documented, mainly in Germany (Amann, 1979a&b; Amann, 1982; Turner & Mills, 1993) which investigated the use of agnus castus to treat symptoms of corpus luteum deficiency such as irregular menstrual cycles, dysfunctional uterine bleeding, mastopathy, premenstrual syndrome, and acne. Results of the studies have indicated that agnus castus can have a beneficial effect when administered to women aged 20-40 years of normal weight, whose ovarian function is not too impaired, and who do not have additional hormonal imbalances such as disorders of thyroid function or prolactin metabolism, or adrenocortical abnormalities (Amann, 1979a&b). Agnus castus has also been reported to be effective in the treatment of endocrine disorders such as menstrual neuroses and dermatoses (Kartnig, 1986), and has been used in the treatment of acne (Amann 1975 & 1984). In addition, a lactogenic

action has been documented with chemical analysis reporting no changes in the breast milk composition (Bruckner, 1989).

The documented constituents of agnus castus are unremarkable consisting of flavonoids, essential oil with cineol and pinene as the main components, a bitter compound, and an alkaloid of unknown type termed viticin (Newall et al, 1996). The constituents responsible for the observed pharmacological actions are unclear. Indeed, the precise mode of action of agnus castus has not been established, although it is thought to act on the pituitary-hypothalamic axis rather than directly on the ovaries. Results of animal studies have reported that agnus castus diminishes the release of follicle stimulating hormone from the anterior pituitary whilst increasing the release of luteinising hormone (Amann, 1966; Houghton, 1994d). In the UK, an agnus castus product is licensed as "a traditional herbal remedy to help restore normal fluid balance and relieve occasional bloatedness in women" (Anderson, 1997).

5.3.2 Echinacea (*Echinacea* spp.)

Echinacea (*Echinacea* spp.) is a perennial herb originating from western United States and cultivated as an ornamental plant in Europe (Mills, 1985). The root and rhizome are used in herbal medicine and are reputed to possess antiseptic, antiviral and peripheral vasodilator properties (Newall et al, 1996). Animal studies have reported various activities including anti-inflammatory, antiviral, antitumour, antibacterial and immunostimulant. Echinacea contains a variety of documented constituents including alkaloids (saturated pyrrolizidine), amides, sesquiterpene lactones, polyacetylenes, phenolic acid glycosides, and high molecular weight polysaccharides (HMWPs). Echinacea is one of a number of plants, including arnica, calendula, chamomile, ginseng, marshmallow and saw palmetto, for which observed immunostimulant activity has been attributed to HMWP components (Wagner, 1987). It is thought that these plant extracts influence mainly unspecified cellular and/or humoral immune defence mechanisms. Activity is therefore assessed by various *in vitro* and *in vivo* test systems measuring the effect of the extracts on granulocyte and macrophage phagocytosis,

lymphocyte activity, and on the liberation of mediators such as interferon, prostaglandins and lymphokines (Wagner, 1987). Echinacea has been used for its non-specific action on cell-mediated immunity. A single 2mL subcutaneous injection followed by a free interval of one week was reported to stimulate cell-mediated immunity, whereas daily administration of the injection was stated to have a depressant effect (Westendorf, 1982). Examples of licensed indications permitted for echinacea-containing medicinal products in the UK include "symptomatic relief of colds and upper respiratory tract infections" and "symptomatic relief of minor skin conditions, acne, and minor eczema" (Anderson, 1997).

5.3.3 Evening Primrose (*Oenothera biennis*)

Interest in the seed oil of evening primrose (*Oenothera* spp) lies in its essential fatty acid content, in particular in the linoleic acid (LA) and gamolenic acid (GA) content. Both of these compounds are prostaglandin precursors and dietary GA supplementation has been shown to increase the ratio of non-inflammatory: inflammatory prostaglandin compounds (Horrobin, 1990). The use of evening primrose oil in various disease states associated with low GA concentrations has been extensively investigated and a vast body of published literature is available. The use of evening primrose oil has been investigated in many disease states including atopic eczema, premenstrual syndrome including mastalgia, diabetic neuropathy, rheumatoid arthritis, Sjogrens Syndrome, cardiovascular, renal, hepatic and gastro-intestinal disorders, viral infections, endometriosis, schizophrenia, alcoholism, Alzheimer's disease, and cancers (Horrobin, 1990; Newall, 1996). The beneficial effects of evening primrose oil in treating atopic eczema and mastalgia (cyclical/non-cyclical) have been recognised with product licences granted to evening primrose oil-containing preparations for these indications (Anon, 1995c). However, doubt has also been expressed over the effectiveness of evening primrose oil in eczema (Anon, 1990a; Bamford et al, 1985; Barber, 1988; Berth-Jones & Graham-Brown, 1993; McHenry et al, 1995).

5.3.4 Feverfew (*Tanacetum parthenium*)

Feverfew (*Tanacetum parthenium*) is a perennial herb that is common throughout central and southern Europe (Mills, 1985). The aerial parts are utilised in herbal medicine and traditionally feverfew has been used in conditions including migraine, tinnitus, rheumatism, fever and menstrual disorders (Newall et al, 1996). Feverfew is characterised by the sesquiterpene lactone constituents, in particular by parthenolide which is thought to be the main active component. Interest in feverfew has centred on its potential role as a prophylactic in migraine. Limited clinical studies have indicated that feverfew may indeed be a useful prophylactic against migraine (Johnson et al, 1985; Murphy et al, 1988), although it has been recommended that feverfew should only be used by sufferers who have proved unresponsive to conventional forms of treatment (Awang, 1993; Berry, 1994). The exact mode of action of feverfew in relieving migraine is unclear, although feverfew has been reported to inhibit granule secretion in blood platelets which is implicated in the aetiology of migraine (Heptinstall et al, 1985). Parthenolide is also reported to interfere with both contractile and relaxant mechanisms in vascular smooth muscle (Knight, 1995). Crude feverfew extracts have also been shown to block voltage-dependent potassium channels selectively in smooth muscle cells, although the significance of this observation with respect to migraine prophylaxis is unclear (Knight, 1995). Other activities reported from animal studies include inhibition of platelet aggregation, of prostaglandin, thromboxane and leukotriene production, and of granule secretion in neutrophils (Capasso, 1986; Collier et al, 1980; Heptinstall et al, 1985; Makheja & Bailey, 1981).Feverfew is thought to inhibit the enzyme phospholipase A_2, which facilitates the release of arachidonic acid from the phospholipase cellular membrane (Capasso, 1986; Makheja & Bailey, 1981&1982). Unfortunately most of the pharmacological studies on feverfew have been *in vitro*. Further studies, both *in vivo* and clinical, are required to establish the efficacy of feverfew in migraine and to gain a clearer understanding of its mechanism of action. Currently there are no licensed feverfew preparations in the UK. The importance of ensuring the quality of feverfew preparations is highlighted by Barsby et al (1993), who studied the effects of extracts of fresh plant and commercial dried powdered leaves on vascular smooth muscle contractility. Whereas the fresh plant extract was found to

inhibit *in vitro* contractile responses to various agonists, the dried powdered leaves extract not only lacked such an inhibitory effect but also elicited potent and sustained contractions. The observed differences were attributed to a lack of sesquiterpene lactone constituents in the dried powdered leaves extract. Interestingly, the sequential treatment of dried powdered feverfew leaf devoid of parthenolide with an oxidant and then a weak base results in the regeneration of substantial amounts of parthenolide (Knight, 1995). Knight (1995) comments that such a reaction may occur *in vivo*.

5.3.5 Ginger (*Zingiber officinale*)

Ginger (*Zingiber officinale*) is perhaps more commonly associated with culinary rather than medicinal uses. However, the underground stem of ginger also has a traditional use as a carminative, diaphoretic and antispasmodic (Newall et al, 1996). These uses are probably attributable to the volatile oil and oleo-resin constituents. Many actions have been reported for ginger from animal studies including hypoglycaemic, hypo- and hypertensive, cardiac, prostaglandin and platelet aggregation inhibition, antihypercholesterolaemic, cholagogic and stomachic (Newall et al, 1996). Particular interest was stimulated in ginger over its potential use as a prophylactic remedy against motion sickness (Grontved et al, 1988; Mowrey & Clayson, 1982; Wood et al, 1988), although conflicting results were reported from these studies. Ginger is currently permitted as a licensed product for the symptomatic relief of travel sickness (Anderson, 1997).

5.3.6 Ginkgo (*Ginkgo biloba*)

The leaf and seed of the *Ginkgo biloba* tree have been used medicinally in China for centuries. Recent European interest in ginkgo stems from the observed activities of the diterpene ginkgolide constituents. Considerable evidence has been documented describing the beneficial actions of ginkgolides on the adverse effects of platelet-activating factor (PAF) in a number of tissues and organs both in animals and humans (Braquet, 1988&1989; Houghton, 1994b). PAF is associated with various negative

effects such as thrombus formation, bronchoconstriction, decreased myocardial contractility and coronary flow, inflammation and vascular permeability, and suppression of T-lymphocyte production. In humans, results of trials in small groups of patients have indicated that ginkgo preparations are effective in the treatment of cerebral and peripheral arterial insufficiency (Pizzorno & Murray, 1985; Vorberg, 1985). Improvements in allergic responses (e.g. asthma) and inhibition of histamine/PAF-induced inflammation and platelet aggregation have also been observed in humans (Braquet, 1987; Chung, 1987). Details have also been documented on the beneficial effects of ginkgo in geriatric illness, including memory impairment (Anon, 1986a; Hindmarsh, 1984), suggesting a potential use in senile dementia. Standardised concentrated extracts of *G.biloba* leaves are marketed in several European countries including France and Germany. Such is the interest in ginkgo, that in 1991 a series of meetings was organised to specifically discuss research into its actions (Christen et al, 1995). At the fifth meeting of this series in 1991, studies investigating the role of a *Ginkgo biloba* extract (Egb 761) in helping functional and anatomical recovery of the brain were presented. Currently there are no licensed ginkgo-containing medicines in the UK. The potential clinical applications of ginkgo are undoubtedly exciting but not suitable for self-medication.

5.3.7 Ginseng (*Eleutherococcus senticosus* & *Panax* spp.)

Ginseng is a generic term that refers to the root of *Eleutherococcus senticosus* and of various *Panax* species. Ginseng has a traditional reputation in Eastern countries as an adaptogen, a substance that is characterised as having three characteristics, namely lack of toxicity, non-specific action, and a normalising action (Farnsworth et al, 1985). An adaptogen is thought to increase the overall resistance of the body to stress and to balance bodily functions. Exstensive investigation has been carried out into the phytochemistry and pharmacological activitiy of ginseng. A broad spectrum of activities have been established in both animal and human studies including hyper/hypoglycaemic, CNS stimulant/depressant, hyper/hypotensive, steroidal, hepatoprotective, cytotoxic and antitumour, antiviral, immunostimulant, and a

favourable effect on psychomotor performance (Newall et al, 1996). The active constituents in ginseng are thought to be the eleutherosides (a heterogeneous mixture of compounds) for Eleutherococcus, and the ginsenosides (triterpenoid saponins) for Panax. The many opposing actions documented for ginseng are thought to support its role as an adaptogen. Traditionally, ginseng root is used in China and Russia to help the body cope with stress and fatigue, and to promote recovery from illness or imbalance such as hypertension or hypoglycaemia. The roots are chewed raw and generally it is only recommended to be used for certain individuals with specific illnesses. By comparison, in the UK ginseng is widely available as an ingredient of food supplements, often in combination with minerals and vitamins.

5.3.8 Saw Palmetto (*Serenoa serrulata*)

The fruit of saw palmetto (*Serenoa serrulata*) is traditionally reputed to possess diuretic, urinary antiseptic, endocrinological and anabolic properties (Newall et al, 1996). The documented constituents of saw palmetto include high molecular weight polysaccharides, fixed oils, and sterols. Phytotherapy is used for the treatment of benign prostatic hypertrophy (BPH) in many countries especially Germany, France, Austria, Switzerland, Spain, Italy and Japan (Buck, 1996). In Austria and Germany, for example, phytotherapy is used as first-line treatment for patients with early and moderate symptoms of BPH and accounts for more than 90% of all drugs prescribed for BPH (Buck, 1996). Of the 30 plant-derived compounds available in Europe for the treatment of BPH, 15 are derived from saw palmetto (Buck, 1996). Studies with saw palmetto have reported beneficial effects in both objective (e.g. frequency of nocturia, urine flow rate) and subjective (e.g. intensity of dysuria, patient's and physician's self-rating) assessments in patients receiving saw palmetto compared to placebo (Champault et al, 1984; Tasca et al, 1985). The efficacy of saw palmetto in BPH has been attributed to anti-androgenic and anti-oedematous activities exhibited in animal studies (Carilla et al, 1984; Carreras, 1987; Stenger et al, 1982; Sultan et al, 1984). BPH is stated to result from prostate accumulation of dihydrotestosterone (converted from testosterone by 5α-reductase), which is thought to be a probable mediator of the hyperplasia acting at the

level of androgen receptor (Carilla et al, 1984). Saw palmetto is thought to act by a possible multisite inhibition of androgen action, via inhibition of dihydrotestosterone binding at androgen receptors, 5α-reductase activity on testosterone, and 3α-ketosteroid reductase activity on dihydrotestosterone (Sultan et al, 1984). The latter action has been implicated in the pathogenesis of prostatic hypertrophy in dogs (Sultan et al, 1984). Clinical trials documented for a proprietary preparation (Permixon) containing a lipid-sterol extract of saw palmetto, have reportedly indicated Permixon (320mg/day) to be as effective as finasteride (5mg/day) in relieving the symptoms of BPH but without the side-effects of impotence and loss of libido (Buck, 1996). However, the studies have generally involved small numbers of patients, been carried out over a short period of time, and reported a significant placebo-effect. Few clinical trials have been documented for whole extracts of saw palmetto. Placebo-controlled, long-term studies involving larger numbers of patients are required to further establish the efficacy of saw palmetto in BPH and to gain an understanding of the precise mechanism of action (Buck, 1996).

5.3.9 St. John's Wort (*Hypericum perforatum*)

St. John's Wort (*Hypericum perforatum*) is a perennial herb that is found throughout the UK, Europe and Asia, as well as North America (Mills, 1985). Traditionally, St. John's wort (SJW) is reputed to possess sedative and astringent properties. SJW contains many phenolic constituents including anthraquinone derivatives, flavonoids, acids and tannins. The documented pharmacology for SJW, including anti-inflammatory and sedative actions, has mainly been attributed to hypericin (an anthraquinone derivative) and to the flavonoid constituents. In addition, photosensitising properties are recognised for hypericin. Recent interest in SJW has focused on its potential antidepressant and antiviral effects.

In Germany, SJW extracts are licensed for the treatment of anxiety and depressive and sleep disorders (Linde et al, 1996). Recently, published clinical trials which compare the effects of pharmaceutical preparations of SJW with placebo and common

antidepressants have been reviewed (Linde et al, 1996). The authors conclude there is evidence that SJW is more effective than placebo for the treatment of mild to moderately severe depressive disorders. The authors go on to recommend that further studies comparing SJW extracts with standard antidepressants in well defined groups of patients and comparing different extracts and doses are needed. The mode of action of SJW in treating depression is not clear, although it was originally considered attributable to hypericin which has been reported to virtually irreversibly inhibit monoamine oxidase in rat brain mitochondria *in vitro* (Suzuki et al, 1984). More recently, however, investigations have reported potent monoamine oxidase inhibitory properties for xanthone and flavonoid constituents (Hostettmann et al, 1995). At the Second International Congress on Phytomedicine, results were presented of two further studies investigating the use of a hypericum extract in depression (Anon, 1996g). One study compared hypericum extract with amitriptyline and reported a more beneficial effect for amitriptyline, but a more favourable side-effect profile for hypericum. The second study comparing hypericum with imipramine reported a slightly more beneficial effect for imipramine. It was reported that hypericum extract is also being investigated clinically for several other conditions, including chronic tension-type headache, seasonal affective disorder and, in a combination preparation with black cohosh (*Cimicifuga racemosa*), for the relief of menopausal symptoms.

Hypericin has recently been reported to exhibit antiviral activity against HIV and hepatitis C (Anon, 1989b, 1995a&b). Hypericin has been shown to inactivate several membrane-containing viruses including retroviruses, both *in vitro* and *in vivo*, although the mechanism of antiviral activity is unclear (Hudson et al, 1994).

5.3.10 Valerian (*Valeriana officinalis*)

Valerian (*Valeriana officinalis*) is a perennial herb found throughout Europe (Mills, 1985) with a long traditional use as a herbal medicine. The underground plant parts (rhizome, root) are utilised and valerian is reputed to possess sedative, mild anodyne, hypnotic, antispasmodic, carminative and hypotensive properties (Newall et al, 1996).

Considerable research into the potential sedative action of valerian has been carried out, and a number of documented studies have described a sedative effect in both normal sleepers and sufferers of insomnia (Anon, 1996j; Balderer & Borbely, 1985; Leathwood & Chauffard, 1983 & 1985; Leathwood et al, 1982 & 1983). Sedative properties documented for valerian have been attributed to the iridoid (valepotriate) and essential oil constituents, with CNS depressant actions documented for both in animal studies. However, the iridoid compounds are highly unstable and probably degrade when taken orally. It is therefore still unclear whether other constituents in valerian contribute towards the sedative effect. Recent investigations into the mechanism of action for the sedative effect of valerian extract have reported an interaction with melatonin binding sites, although the constituents responsible for the binding and the nature of the binding (agonist or antagonist) had not yet been determined (Anon, 1996j). Interestingly, it was also stated that results of *in vitro* studies did not support data from earlier studies which suggested valerian extract may interact with the neurotransmitter γ-aminobutyric acid (GABA) (Anon, 1996j).

In the UK, valerian-containing preparations are licensed for indications such as "symptomatic relief of stresses and strains, irritability, restlessness" and "to promote natural sleep" (Anderson, 1997).

5.4 Clinical Trials

5.4.1 Allopathic Medicines

During the licensing process, all submitted medicinal product licence applications are assessed for efficacy in their intended indications. Prospective market authorisation holders are required to submit many dossiers of data in support of their application, representing the culmination of many years research. The length of the drug development phase has reportedly increased four-fold over the last 30 years, to a current average of 12 years (Auty, 1993). Reasons given for this increase include increased

regulatory demands and the fact that more drugs are developed today for the longterm management of chronic diseases. Toxicological and clinical studies for the latter take longer to complete than for drugs intended for acute conditions. Either way, the drug development phase of a medicinal compound is a lengthy and expensive process, requiring the sponsorship of a major pharmaceutical company. A continuous stream of new chemical entities (NCEs) are required in the research and development (R&D) pipeline to support the high drop-out rate (80-90%) of compounds during the drug development phase, due to unsatisfactory results from clinical, toxicological or pharmaceutical work (Auty, 1993). To maximise the marketing period during which the new compound is patent protected (and therefore earning most revenue), it is essential for the development phase of an NCE to be kept to the absolute minimum. Before clinical studies may commence, pharmaceutical research must establish assay techniques, compound purity, and a single, stable formulation. Furthermore, short-term animal toxicity studies are required in addition to limited absorption, distribution, metabolism and excretion studies, together with mutagenicity and fertility tests (Auty, 1993).

Pre-authorisation clinical work is divided into three phases.

Phase I involves small scale studies using healthy volunteers to establish the pharmacological and biochemical effects of the compound, tolerability, absorption, distribution, metabolism and excretion. Single low doses gradually progress to longer periods of administration with larger doses as confidence is gained in the compound (Auty, 1993).

Compared with Phase I, Phase II studies use more patients (hundreds) who are treated for slightly longer periods of time. The principle aim of Phase II studies is to demonstrate the compound exerts the desired therapeutic effect, to indicate the most effective dose or range of doses, to confirm tolerability, and to establish a side-effect profile so that a risk-benefit assessment may be made (Auty, 1993).

Phase III studies usually involve thousands of patients treated for prolonged periods of time, in conditions more closely resembling everyday clinical practice than in Phase II. Studies in Phase III may also utilise specific patient groups, such as children and the elderly (Auty, 1993).

In Phase II, the formulations are often prototypical of the intended market formulation. During Phase III, the intended market formulation must be used (Howard, 1993).

5.4.2 Herbal Medicines

Of the many herbal medicines currently available in the UK, very few have been subjected to clinical trials. At best limited human pharmacology data may be available, but clinical trials of the nature required for allopathic medicines have not usually been carried out. Reasons for this include lack of the necessary infrastructure and funding to undertake statistically valid trials, the complex chemical nature of natural medicines, and determining suitable endpoints to establish efficacy (Mills, 1993). Current UK legislation permits manufacturers of herbal medicines to base their efficacy claims on bibliographic data, providing suitable data are provided for the quality and safety of the product, and the indications are for non-serious medical conditions. If a herbal medicine does not have a traditional use in a particular condition or is to be indicated for a more serious condition, then full clinical trial data are required. Not surprisingly, the vast majority of herbal medicines in the UK contain herbs with a traditional medicinal use and are licensed for minor conditions.

Funding The clinical development of a medicinal compound is extremely expensive. Costs ranging from $50 million to $231 million have been quoted (Auty, 1993). Financially, a pharmaceutical company would not survive long if all its R&D programmes were geared towards therapeutic markets offering little return on research investments, either because of patient size or market saturation with similar compounds. Companies specialising in "me-too" products incur limited research costs involved in getting their products to the market. For NCEs, the time taken from patent registration

to marketing is paramount since every month of delay eats into the patent protected lifetime of the product. Very few NCEs remain the sole licensed product containing a particular drug substance unless the intended patient group is very small or the manufacturing process is complicated. Commercially justifying the considerable development costs for herbal medicines is extremely difficult. In general, herbal medicine does not have teaching hospitals or research institutes to assist in development, or the financial backing associated with the larger pharmaceutical companies. Naturally-occurring compounds are not patentable. This obviously reduces the financial incentives to invest in the development of herbal medicines. Furthermore, in general the market size for many herbal medicines is small compared to that for allopathic drugs (Mills, 1993). This may be the general situation in the UK but in other countries, especially within Europe, there is a considerable market for phytomedicines. In Germany for example, the 1986 annual estimated cost of plant products used to treat benign prostatic hypertrophy (BPH) was estimated at DM 131 million; in Italy plant extracts represent 48.6% of all prescriptions for BPH, compared to 5.1% and 4.8% for alpha-blockers and 5α-reductase inhibitors, respectively (Buck, 1996). A good example within the UK of a commercially successful phytomedicine is evening primrose. Considerable research investment has enabled evening primrose oil to obtain licensed indications for symptomatic treatment of atopic eczema and mastalgia (cyclical/non-cyclical) (Anon, 1995c).

Published research often suffers from poor methodologies and statistical validity, and commonly appears in obscure scientific journals rather than in mainline medical journals such as The Lancet and British Medical Journal. The Research Council for Complementary Medicine was formed in the late 1980's, one of its aims being to improve the quality and quantity of research within complementary medicine (Lewith & Aldridge, 1993). The Centre for Complementary Research, based at Exeter University, was set up in 1987 to study acupuncture, chiropractic, homoeopathy, medical herbalism, naturopathy and osteopathy, and the relationship of these therapies to orthodox medicine (Anon, 1987b). One of the first stated priorities of the centre was to investigate new research techniques

Chemical Complexity A herbal medicine, even single ingredient, represents a complex mixture of pharmacologically active constituents. In contrast, the majority of allopathic medicines contain single, well-defined active constituents. The complex nature of a herbal medicine presents many problems when trying to establish the pharmacological actions of the total mixture. Actions observed with isolated constituents will not equal those of the whole extract. Differences in the type of extract used will also affect observed actions. Unfortunately, when a number of human studies have been performed for a herbal medicine (e.g. valerian), the type of extract used often differs from study to study thereby statistically invalidating a comparison of study results. Reproducible pharmacological activity of a herbal medicine is difficult to guarantee unless the actions can be associated with a major constituent type on which the product is standardised, as with senna products that are usually standardised on their sennoside B content. Because of the many difficulties encountered in the development of a herbal medicine, pharmaceutical companies mainly concentrate efforts on isolating active constituents from the herbal ingredient, which can then be manufactured synthetically.

Suitable Entry Criteria / Endpoints Herbs have traditionally been applied in a qualitatively different way from conventional medicines (Mills, 1993). Whereas conventional medicines are usually aimed at treating a specific symptom perhaps irrespective of the underlying cause, herbal medicine considers the broader picture of an individual in which the presenting symptom is one of many factors considered. The aim of a herbal medicine may often be to restore the recuperative capabilities of the patient, rather than to treat a specific symptom. In addition, a herbal medicine is usually designed specifically for an individual patient rather than a common formula being applied to many individuals. Clinical trials conventionally use specific entry criteria to ensure a suitable patient population, and base efficacy of a compound on a series of specific, measurable endpoints. Determination of specific entry criteria and endpoints in the conventional manner may not be possible for certain herbal medicines such as ginseng, whose claimed adaptogen action is non-specific and may apply to a diverse group of individuals.

5.5 Discussion

In developed countries, every individual has the freedom of choice to select their form of medical care. In the UK, the form of care chosen automatically by the majority of individuals is conventional medicine. However, an increasing number are selecting alternative types of care either in addition to or in preference to conventional medicine. The published results of a number of surveys carried out in the UK during the 1980's indicated herbal medicine to be one of a number of popular complementary therapies (see Chapter 1) (Sharma, 1992). The use of herbal medicine may involve self-medication with off-the-shelf remedies, self-collection of plants, or consultation with a medical herbalist. This discussion is concerned with the former option only.

The hazards associated with any form of self-medication centre on appropriate diagnosis by the individual, efficacy of the remedy chosen for self-medication, cessation of any orthodox treatment in favour of self-help, potential interaction between an existing orthodox medicine and a self-medicated remedy, and delay in seeking professional medical advice.

The significance of whether or not a herbal remedy actually works obviously depends on the nature of the medical condition being treated. Many herbal remedies are used to treat minor, non-life threatening conditions. Despite a dearth of documented clinical data for the majority of herbal ingredients, there is no reason why they should not be available for minor conditions (i.e. suitable for self-diagnosis and treatment), providing these conditions are consistent with traditional uses of the herb and that the herbal ingredients are of a suitable quality and safety. It would seem more appropriate to use those herbal ingredients for whom documented phytochemical and pharmacological data support the traditional uses. The current UK medicines legislation permits bibliographic data to be used as proof of efficacy for herbal medicines intended for minor conditions.

The use of a herbal remedy in a more serious condition is of greater concern. If a herbal medicine is to be indicated for a more serious condition then the necessary supporting

animal and clinical data must be provided. This is claimed to be commercially non-feasible for the majority of herbal medicine manufacturers and therefore most herbal medicines remain licensed for minor medical conditions based on traditional uses.

However, doctors may well be faced with patients wishing to use a herbal remedy for an unlicensed use. It is difficult to stop an individual making such a choice and therefore it is important that any such decision taken by a patient is an informed one and is not based upon unsubstantiated claims of efficacy. A doctor is not only in a position to advise a patient on the risks of stopping their conventional medicine (if this is what is proposed), but is also able to seek available information on the particular herbal remedy. A lack of evidence regarding efficacy is one concern, but exposure to additional hazards via the quality of a remedy or the inherent toxicity of a herbal ingredient must also be considered. At least if a doctor is aware of a patient's intentions, appropriate advice and action may be undertaken.

In addition to doctors, pharmacists are facing a greater involvement in the use of herbal remedies. Many pharmacies now stock a range of herbal products and, logically, the pharmacist should be able to offer professional advice on their use as medicines. It is also important for the pharmacist to be aware of the potential problems involved in supplying unlicensed herbal remedies, of which there are many, so that some informed discretion can be exercised when deciding on which herbal products to stock. In addition to herbal remedies offered for sale in their pharmacy, pharmacists may well be asked their professional opinion on products purchased from other retail outlets such as healthfood stores and supermarkets. The pharmacist is perceived by the general public, and rightly so, as being able to offer unbiased professional advice on products purchased as medicines. In order to live up to this perception for herbal products, it is important for pharmacists to remain abreast of any issues surrounding the use of herbal remedies and to be aware of available information sources.

It is clear that plants offer a wealth of pharmacologically active constituents and potentially clinically beneficial compounds. However there is no shortcut to identifying and establishing the true usefulness of such compounds, and research and development

requires the significant financial backing of major pharmaceutical manufacturers or other funding organisations. Not surprisingly phytochemical investigations concentrate on the identification and isolation of bioactive constituents using an infrastructure of suitable bioassays, separation techniques, and methods for structure determination (Hostettmann et al, 1995). Knowledge of activities associated with particular chemical groups of constituents combined with known traditional uses, can assist in focusing the choice of plants to investigate. The investigation and development of whole plant extracts is fraught with difficulties of standardisation and bioequivalence and is not usually pursued. The recent licence application by Phytopharm for its 10-herb eczema preparation, based on a combination of herbs used in traditional Chinese medicine, is a rare exception (Anon, 1996c). The granule preparation is currently undergoing phase III clinical trials. Clinical studies may be able to demonstrate the efficacy of a plant in a particular disease state, without necessarily understanding the mechanism of action or responsible plant constituents. Since the pharmacological activities of a plant are often attributable to more than one constituent type, it is difficult to choose an individual constituent on which to standardise a preparation. Nevertheless, many plant extracts are standardised on a specific constituent or constituent type, such as ginsenosides for ginseng, hypericin for St. John's wort, ginkgolides for ginkgo, parthenolide for feverfew, aescin for horse-chestnut. Whilst such standardisation may offer guarantees of quality control and is therefore important, it will not necessarily guarantee bioequivalence between preparations. Clinical trials are required to establish the latter.

The recent overview of published clinical trials for St. John's wort (SJW) in the treatment of depression highlights many difficulties encountered when investigating the efficacy of a herbal medicine (Linde et al, 1996). Despite the existence of 23 published trials (which met the criteria of the reviewers) involving some 1757 patients, conclusions could still not be reached over the true efficacy of SJW in depression. The independence of the research groups performing the trials resulted in inconsistencies of methodology which made cross-trial comparison difficult. Examples of these inconsistencies include varied entry criteria (e.g. inconsistent classification of depression), variety of SJW preparations employed, variation in the dose of hypericin (on which many preparations are standardised) or of total extract employed (between

0.4 - 2.7mg hypericin and 300mg-1000mg total extract), and doubt over successful blinding (e.g. fluid preparations which would have a distinctive taste were used in some trials). The constituent(s) responsible for the antidepressive action of SJW is unclear. Hypericin standardisation may result in preparations with varied levels of other constituents that may contribute to the antidepressive effect, such as flavonoids.

Clearly, for herbal medicines to be used alongside conventional medicines as treatment options for more serious medical conditions, considerable research and development investment from the major pharmaceutical companies is required. The traditional uses currently permitted for licensed herbal medicines on the basis of bibliographic data only represent the more minor medical conditions that are considered suitable for self-diagnosis and self-treatment. In order to select a herbal medicine over a conventional medicine, a prescriber needs to be confident of the therapeutic effect of a particular herbal preparation at a specific dose, and be able to compare this effect to that of existing drug options. This confidence can only be gained from the results of clinical trials, perhaps in comparison with existing conventional treatments.

6. INFORMATION SOURCES AND REQUIREMENTS OF HERBAL REMEDIES

6.1 Methods

6.1.1 Identification of Herbal Remedies and Herbal Ingredients

Herbal Remedies

- The alphabetical product listing in the Chemist and Druggist price list was studied and all herbal products were noted together with their listed manufacturer.
- A letter was published in the Pharmaceutical Journal (Phillipson & Anderson, 1986) appealing to pharmacists for information on both herbal products stocked and those for which there was considerable public demand.
- Popular health magazines, e.g. Here's Health and Healthy Living, were regularly scanned for details of manufacturers placing advertisements for herbal products.
- A number of pharmacies (ca. 30) and key healthfood stores were visited in and around the London area to check for any additional manufacturers not identified by the previous methods.

Herbal Ingredients

- Letters were sent to the identified manufacturers requesting details on their herbal products.
- In the order of 30 pharmacies and key healthfood stores in and around the London area were visited, to obtain details of the herbal ingredient constituents of identified herbal products.

6.1.2 Information Sources on Herbal Ingredients

The categories of information sources on herbal ingredients used in this investigation included pharmacopoeias, scientific and non-scientific books, primary and secondary literature, and on-line databases. Examples of the sources used within these categories are listed in Table 6.1.

Table 6.1 Examples of Information Sources on Herbal Ingredients

Examples of Information Sources on Herbal Ingredients
Pharmacopoeias
British Herbal Pharmacopoeia (Anon, 1996t)
British Pharmaceutical Codex (Anon, 1973)
European Pharmacopoeia (Anon, 1997a)
Martindale, The Extra Pharmacopoeia (Anon, 1996a)
Scientific
A Colour Atlas of Poisonous Plants (Frohne & Pfander, 1984)
Adverse Effects of Herbal Drugs Vol. 1&2 (DeSmet et al, 1992&1993)
Botanical Dermatology (Mitchell & Rook, 1979)
Casarett & Doull's Toxicology: The Basic Science of Poisons (Anon, 1996v)
Encyclopedia of Common Natural Ingredients used in Food, Drugs and Cosmetics (Leung, 1980)
Essential Oil Safety (Tisserand & Balacs, 1995)
Herbal Drugs and Phytopharmaceuticals (Bisset, 1994)
Herbs - An Indexed Bibliography (Simon et al, 1984)
Trease & Evans' Pharmacognosy (Evans, 1996)

Examples of Information Sources on Herbal Ingredients
Selected Medicinal Plants (Morelli, 1983) Taschenbuch der drogenkunde (Hoppe, 1981) The Essential Oils (Guenther, 1948-1952) The Merck Index: an encyclopedia of chemicals, drugs and biologicals (Anon, 1996u)) Plant Drug Analysis (Wagner et al, 1983)
Primary Literature British Journal of Pharmacology British Medical Journal Chemical and Pharmaceutical Bulletin Economic Botany European Journal of Pharmacology Fitoterapia Herbalgram Human Toxicology Journal of Alternative Medicine Journal of Ethnopharmacology Journal of Natural Products (Lloydia) Journal of Pharmacy and Pharmacology Journal of Pharmaceutical Science Journal of Toxicology and Environmental Health Lancet Lawrence Review of Natural Products Pharmaceutical Journal Pharmacy International Phytochemistry Phytotherapy Research Planta Medica

Examples of Information Sources on Herbal Ingredients
Secondary Literature
Chemical Abstracts
Current Advances in Plant Science
Current Contents Life Sciences
International Pharmaceutical Abstracts
Index Medicus
On-Line Databases
Biological Abstracts
Chemical Abstracts
Excerpta Medica
Medline

6.1.3 Information Needs of the Pharmacist

In order to ascertain the nature of enquiries received by pharmacists on herbal medicines, and therefore their information needs, a visit was made to the Welsh Drug Information Centre (WDIC) at Cardiff Heath Hospital. The WDIC holds the specialist drug information file on alternative medicine and receives enquiries not only from Wales but also from all other regional drug information centres in the UK. Over a two day period, microfiche files were searched to obtain details on the number and category of alternative medicine enquiries received during 1986. The enquiries involving herbal medicine were identified and their respective hard copies retrieved to note further information. All enquiries which fell into the "general" category were also checked for any reference to herbal medicine.

6.2 Results

6.2.1 Identification of Herbal Remedies and Herbal Ingredients

No response was received to the letter placed in the Pharmaceutical Journal (Phillipson & Anderson, 1986).

Details were obtained for a total of 623 different products from 37 manufacturers, involving some 200 herbal ingredients. The manufacturers together with their number of identified products are listed in Table 6.2.

Table 6.2 Identified Herbal Manufacturers

Manufacturer	No. Products Identified	Manufacturer	No. Products Identified
Arkopharma (UK) Ltd.	55	Hofels Pure Foods Ltd.	12
Bio Health	1	House of Mistry	4
Blackmores Lab. Ltd.	28	Jessup Marketing	7
Booker Health	78	Larkhall Lab. (Cantassium)	46
Boots Company Ltd.	1	Lifeplan Products	16
Britannia Health Products Ltd.	3	Modern Health Products Ltd.	5
Celaton Lab. Research Ltd.	26	Modern Products Inc.	3
Dietary Specialities	4	Nature's Own	4
Dr. Dunner	3	Ortis of Belgium	3
English Grains	32	Pharmadass	16

Manufacturer	No. Products Identified	Manufacturer	No. Products Identified
Evening Primrose Oil Co. Ltd.	1	Pharmaton	2
Food Supplement Co.	22	Potters	46
GR Lane Health Products Ltd.	11	Power Health Products Ltd.	30
Gerard House	35	Salus-Haus	15
Green Farm Nutrition Centre	18	Seven Seas	11
Healtheries	30	Vessen Ltd.	6
Healthilife Ltd.	13	Vitabiotics Ltd.	3
Herbal Laboratories	20	Vitalia Ltd.	9
		Vitalife	4

The final list of 141 herbal ingredients for which it was decided to collate information is presented in Table 6.3. Herbs present in many products, in particular herbal teas, but for which factual information is readily available, e.g. blackcurrant, peppermint, rosehip, were not included in the final list. In addition, herbs present in only one or two obscure products were also excluded from the final list.

Table 6.3 141 Herbal Ingredients On Which Information Was Collated

141 Herbal Ingredients On Which Information Was Collated					
Agnus Castus	Calendula	Drosera	Guaiacum	Myrrh	Scullcap
Agrimony	Capsicum	Echinacea	Hawthorn	Nettle	Senega
Alfalfa	Cascara	Elder	Holy Thistle	Parsley	Senna
Aloe Vera	Cassia	Elecampane	Hops	Parsley Piert	Shepherd's Purse

141 Herbal Ingredients On Which Information Was Collated					
Aloes	Celery	Eucalyptus	Horehound, Black	Passion Flower	Skunk Cabbage
Angelica	Centaury	Euphorbia	Horehound, White	Pennyroyal	Slippery Elm
Aniseed	Cereus	Evening Primrose	Horse-Chestnut	Pilewort	Squill
Apricot	Chamomile, German	Eyebright	Horseradish	Plantain	St. John's Wort
Arnica	Chamomile, Roman	False Unicorn	Hydrangea	Pleurisy Root	Stone Root
Artichoke	Chaparral	Fenugreek	Hydrocotyle	Pokeroot	Tansy
Asafoetida	Cinnamon	Feverfew	Ispaghula	Poplar	Thyme
Avens	Clivers	Figwort	Jamaica Dogwood	Prickly Ash, Northern	Uva-Ursi
Bayberry	Clove	Frangula	Juniper	Prickly Ash, Southern	Valerian
Bloodroot	Cohosh, Black	Fucus	Lady's Slipper	Pulsatilla	Vervain
Blue Flag	Cohosh, Blue	Fumitory	Lemon Verbena	Quassia	Wild Carrot
Bogbean	Cola	Garlic	Liferoot	Queen's Delight	Wild Lettuce
Boldo	Coltsfoot	Gentian	Lime Flower	Raspberry	Willow
Boneset	Comfrey	Ginger	Liquorice	Red Clover	Witch Hazel
Borage	Corn Silk	Ginkgo	Lobelia	Rhubarb	Yarrow
Broom	Couchgrass	Ginseng, Eleuthero-coccus	Marshmallow	Rosemary	Yellow Dock
Buchu	Cowslip	Ginseng, Panax	Mate	Sage	Yucca
Burdock	Damiana	Golden Seal	Meadow-sweet	Sarsaparilla	
Burnet	Dandelion	Gravel Root	Mistletoe	Sassafras	
Calamus	Devil's Claw	Ground Ivy	Motherwort	Saw Palmetto	

6.2.2 Information Needs of the Pharmacist

Of the total number of enquiries received by the WDIC on alternative medicine during 1986, over 56% related to herbal medicine (Table 6.4).

When comparing the types of enquiries received (Table 6.5) three main areas of concern were observed, namely adverse effects (40.3%), pharmacology (26.6%), and identification (13.6%). The majority of queries on adverse effects and interactions were questioning the possibility of a particular reaction rather than recording the occurrence of an actual event. The high percentage of enquiries regarding identification highlighted the problem of poorly labelled products. The 154 enquiries involved 44 different products and 74 herbs, the three most popular herbs being evening primrose, feverfew, and ginkgo.

Table 6.4 Alternative Medicine Enquiries Received by the Welsh Drug Information Centre During 1986

Category	Number of Enquiries	%
Herbal	154	56.6
Homoeopathic	47	17.3
Vitamin/Mineral	28	10.3
Miscellaneous[1]	43	15.8
Total	**272**	**100**

[1] Included any queries on health foods, alternative medicine in general, or where the subject matter was not clearly defined

Table 6.5 Distribution of Enquiry Types on Herbal Medicine

Enquiry Type	Herbal (n = 154)	
	n[1]	%
Administration/Dose	7	4.5
Adverse Effects	62	40.3
Availability/Supply	12	7.8
Choice of Therapy	10	6.5
Identification	21	13.6
Interactions	9	5.8
Pharmaceutical	2	1.3
Pharmacology	41	26.6
Poisoning	4	2.6
Other[2]	22	14.3

[1] Enquiries may fall into more than one category
[2] Included general enquiries and product information requests

Areas of particular concern highlighted by the enquiries were use of herbal products during pregnancy and lactation, potential drug/herb interactions, and appropriate doses of herbs for children. Examples of some of the queries are listed in Table 6.6.

Table 6.6 Examples of Enquiries Received by the Welsh Drug Information Centre on Herbal Medicine

Can aniseed cause thrombocytopenia?
Ginkgo biloba extract - use in Alzheimer's Disease and general information
Constituents and use of agnus castus in endometriosis
Which herbal remedies could interfere with warfarin?
Dose of feverfew capsules for migraine?

Does agrimony affect thyroid function?
Can devil's claw cause GI bleeding?
Any GI side-effects of lupulus taken with lecithin, passiflora and jamaica dogwood?
Any interaction between Nardil and Quiet Life Tablets?
Any renal effects of Grangewood insomnia tablets?
Can feverfew be taken in pregnancy?

The information categories which it was decided to include in the herbal monographs are listed in Table 6.7.

Table 6.7 Categories of Information Included in the Herbal Ingredient Monographs

Category	Information Provided
Monograph Title	Common name for the herbal ingredient; if more than one common name exists, this is the chosen preferred name.
Species (Family)	Preferred botanical name with authority, together with the plant family.
Synonyms	Other common or botanical names.
Part(s) Used	Plant part(s) traditionally used in herbal medicine.
Pharmacopoeial Monographs	Key pharmacopoeial monographs, with special emphasis on European national pharmacopoeias.
Legal Category	Legal category of the herbs with respect to licensed products. For the majority of herbal ingredients this will be GSL.
Constituents	Main documented chemical constituents grouped into categories such as alkaloids (type specified), flavonoids, iridoid

Category	Information Provided
	glycosides, saponins, tannins, triterpenes, volatile oil and "other constituents" for miscellaneous and minor chemical components.
Food Use	Provides an indication as to whether the herbal ingredient is used in foods. Council of Europe (COE) category (N1 to N4) quoted where applicable which reflects the opinion of the COE on the suitability of the herbal ingredient for use as a food flavouring. Also where applicable, the FDA listing is stated, e.g. "Generally Regarded as Safe" (GRAS), and "Herb of Undefined Safety".
Herbal Use	States the reputed actions and uses of the herbal ingredient. For many of the monographs this section refers to the British Herbal Pharmacopoeia (BHP). In some instances current investigations are included.
Dose	States the traditional dose of the herbal ingredient, mainly from the BHP, giving doses for plant part used (herb, rhizome, leaf), liquid extract and infusion.
Pharmacological Actions	Describes any documented pharmacological actions for the herbal ingredient in both animals(*in vivo* or *in vitro*) or humans.
Side-Effects, Toxicity	Details any documented side-effects to the herbal ingredient and any toxicological studies. Includes side-effects or toxicity that are generally associated with any of the constituents in the herbal ingredient or with its plant family.
Contra-indications, Warnings	Describes any potential contra-indications and warns against any potential side-effects and any individuals who may be more susceptible. Comments on use during pregnancy and lactation are included.
Pharmaceutical Comment	Provides overall summary of the monograph, indicating the extent of the available phytochemical and pharmacological

Category	Information Provided
	data, whether or not proposed uses are justified by these data, any concerns over safety, and general suitability of the herbal ingredient for use as a herbal remedy.
References	Specific references included at the end of each monograph, together with any general reference sources used.

The herbal monograph for Uva-ursi is shown in Figure 6.1. Uva-ursi is an example of a common herbal ingredient of herbal remedies, for which there is information documented under all of the category headings listed in Table 6.7.

Figure 6.1 **Herbal Monograph for Uva-ursi**

UVA-URSI

Species (Family)
Arctostaphylos uva-ursi (L.) Spreng (Ericaceae)

Synonym(s)
Bearberry

Part(s) Used
Leaf

Pharmacopoeial Monographs
BHP 1983
BHP 1990
BPC 1934
Martindale 30th edition
Pharmacopoeias – Aust., Cz., Egypt, Fr., Ger., Hung., Jpn, Rus., Swiss, and Yug.

Legal Category (Licensed Products)
GSL[G43]

Constituents[G4,G7,G8,G9,G10,G12]
Flavonoids Flavonols (e.g. myricetin, quercetin) and their glycosides including hyperin, isoquercitrin, myricitrin, and quercitrin.
Iridoids Asperuloside (disputed), monotropein[1]
Quinones Total content at least 6%, mainly arbutin (5–15%) and methyl-arbutin (glycosides), with lesser amounts of piceoside[2] (a glycoside), free hydroquinone and free *p*-methoxyphenol[3]
Tannins 6–7% (range 6–40%). Hydrolysable-type (e.g. corilagin pyranoside), ellagic and gallic acids (usually associated with hydrolysable tannins)
Terpenoids α-Amyrin, α-amyrin acetate, β-amyrin, lupeol, uvaol, ursolic acid, and a mixture of mono- and di- ketonic α-amyrin derivatives[4,5]
Other constituents Acids (malic, quinic), allantoin, resin (e.g. ursone), volatile oil (trace), wax
Other plant parts The root is reported to contain unedoside (iridoid glucoside).[6]

Food Use
Uva-ursi is not used in foods.

Herbal Use
Uva-ursi is stated to possess diuretic, urinary antiseptic, and astringent properties. Traditionally, it has been used for cystitis, urethritis, dysuria, pyelitis, lithuria, and specifically for acute catarrhal cystitis with dysuria and highly acidic urine.[G1,G2,G3,G4,G5]

Dose
Dried leaves 1.5–4.0 g or by infusion three times daily[G2,G3]
Liquid Extract 1.5–4.0 mL (1:1 in 25% alcohol) three times daily[G2,G3]
Concentrated Infusion of Bearberry (BPC 1934) 2–4 mL
Fresh Infusion of Bearberry (BPC 1934) 15–30 mL

Pharmacological Actions
Animal studies Uva-ursi has exhibited antimicrobial activity towards a variety of organisms including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Mycobacterium smegmatis*, *Shigella sonnei*, and *Shigella flexneri*.[7] The antimicrobial activity of arbutin towards bacteria implicated in producing urinary-tract infections, has been found to be directly dependent on the β-glucosidase activity of the infective organism.[8] Highest enzymatic activity was shown by *Enterobacter*, *Klebsiella*, and *Streptococcus* genera, and lowest by *Escherichia coli*.[8] The minimum inhibitory concentration for arbutin is reported to be 0.4–0.8% depending on the micro-organism.[8] Aqueous and methanolic extracts have demonstrated molluscicidal activity against *Biomphalaria glabrata*, at a concentration of 50 ppm.[9] The activity was attributed to the tannin constituents (condensed and hydrolysable).
Anti-inflammatory activity (rat paw oedema tests) has been documented for uva-ursi against a variety of chemical inducers such as carrageenan, histamine, and prostaglandins.[10]
Uva-ursi failed to exhibit any *in-vitro* uterotonic action when tested on rabbit and guinea-pig uteri.[11]
Hydroquinone has been reported to show a dose-dependent cytotoxic activity on cultured rat hepatoma cells (HTC line); arbutin was not found to inhibit growth of the HTC cells.[12] It was stated that hydroquinone appeared to have greater cytotoxic activity towards rat hepatoma cells than agents like azauridin or colchicine, but less than valtrate from valerian (*Valeriana officinalis*). The cytotoxicity of hydroquinone has also been tested on L1210, CA-755, and S-180 tumour systems.[12]
Human studies A herbal preparation, whose ingredients included uva-ursi, hops, and peppermint, has been used to treat patients suffering from compulsive strangury, enuresis, and painful micturition.[13] Of 915 patients treated for six weeks, success was reported in about 70%. The antiseptic and diuretic properties claimed for uva-ursi can be attributed to the hydroquinone derivatives, especially arbutin. The latter is absorbed from the gastro-intestinal tract virtually unchanged and during renal excretion is hydrolysed to yield the active principle, hydroquinone, which exerts an antiseptic and astringent action on the urinary mucous membranes.[14,15] The crude extract is reported to be more effective than isolated arbutin as an astringent and antiseptic.[G24] This may be due to the other hydroquinone derivatives, in addition to arbutin, that are present in the crude extract and which will also yield hydroquinone. Furthermore, it has been stated that the presence of gallic acid in

Figure 6.1 Herbal Monograph for Uva-ursi (cont.)

the crude extract may prevent β-glucosidase cleavage of arbutin in the gastro-intestinal tract before absorption, thereby increasing the amount of hydroquinone released during renal excretion.[G74]

Side-effects, Toxicity

No reported side effects were located. Hydroquinone is reported to be toxic if ingested in large quantities: 1 g (equivalent to 6–20 g plant material) has caused tinnitus, nausea and vomiting, sense of suffocation, shortness of breath, cyanosis, convulsions, delirium and collapse.[G74] A dose of 5 g (equivalent to 30–100 g of plant material) has proved fatal.[G74] In view of the high tannin content, prolonged use of uva-ursi may cause chronic liver impairment.[G39]

Cytotoxic activity has been documented for hydroquinone (*see* Animal studies).

Uva-ursi herb can sometimes be adulterated with box leaves (*Buxus sempervirens*), which contain toxic steroidal alkaloids. However, no cases of poisoning as a result of such adulteration have been reported.[G43]

Contra-indications, Warnings

Uva-ursi requires an alkaline urine for it to be effective as a urinary antiseptic; an alkaline reaction is needed to yield hydroquinone from the inactive esters such as arbutin.[13] Patients have been advised to avoid eating highly acidic foods, such as acidic fruits and their juices.[13] The presence of hydroquinone may impart a greenish-brown colour to the urine, which darkens following exposure to air due to oxidation of hydroquinone.

Excessive use of uva-ursi should be avoided in view of the high tannin content and potential toxicity of hydroquinone.

Prolonged use of uva-ursi to treat a urinary-tract infection is not advisable. Patients in whom symptoms persist for longer than 48 hours should consult their doctor.

Pregnancy and lactation. Large doses of uva-ursi are reported to be oxytocic,[G40] although *in-vitro* studies have reported a lack of uteroactivity. In view of the potential toxicity of hydroquinone, the use of uva-ursi during pregnancy and lactation is best avoided.

Pharmaceutical Comment

The chemistry of uva-ursi is well documented with hydroquinone derivatives, especially arbutin, identified as the major active constituents. Documented pharmacological actions justify the herbal use of uva-ursi as a urinary antiseptic. However, clinical information is lacking and further studies are required to determine the true usefulness of uva-ursi in the treatment of urinary-tract infections. Although hydroquinone has been reported to be toxic in large amounts, concentrations provided by the ingestion of therapeutic doses of uva-ursi are not thought to represent a risk to human health.[G20]

References

See General References G1, G7, G13, G14, G15, G40, G43, G44, G49, G70, G72, G74, G81, and G82.

1. Jahodar L *et al.* Investigation of iridoid substances in *Arctostaphylos uva-ursi*. *Pharmazie* 1978; **33:** 536–7.

2. Karikas GA *et al.* Isolation of piceoside from *Arctostaphylos uva-ursi*. *Planta Med* 1987; **53:** 307–8.

3. Jahodar L, Leitertova I. The evaluation of *p*-methoxyphenol in the leaves of *Arctostaphylos uva-ursi*. *Pharmazie* 1979; **34:** 188–9.

4. Drobac A. Triterpenes of *Arctostaphylos uva-ursi* Spreng. *Plant Med Phytother* 1980; **14:** 155–8.

5. Mallerud KE. The non-polar components of *Arctostaphylos uva-ursi* leaves. *Medd Nor Farm Selsk* 1980; **42:** 15–20.

6. Jahodar L *et al.* Unedoside in *Arctostaphylos uva-ursi* roots. *Pharmazie* 1981; **36:** 294–6.

7. Moskalenko SA. Preliminary screening of far-Eastern ethnomedicinal plants for antibacterial activity. *J Ethnopharmacol* 1986; **15:** 231–50.

8. Jahodar L *et al.* Antimicrobial action of arbutin and the extract from the leaves of *Arctostaphylos uva-ursi* in vitro. *Ceskoslov Farm* 1985; **34:** 174–8.

9. Schantelberger D, Hostettmann K. On the molluscicidal activity of tannin containing plants. *Planta Med* 1983; **48:** 105–7.

10. Shipochliev T, Tournadiev G. Spectrum of the antiinflammatory effect of *Arctostaphylos uva ursi* and *Achilea millefolium*. L. *Probl Vutr Med* 1984; **12:** 99–107.

11. Shipochliev T. Extracts from a group of medicinal plants enhancing the uterine tonus. *Vet Med Nauki* 1981; **18:** 94–8.

12. Assaf MH *et al.* Preliminary study of the phenolic glycosides from *Origanum majorana*: quantitative estimation of arbutin; cytotoxic activity of hydroquinone. *Planta Med* 1987; **53:** 343–5.

13. Lenau H *et al.* Wirksamkeit und Vertraglichkeit von Cysto Fink bei Patienten mit Reizblase und/oder Harninkontinenz. *Therapiewoche* 1984; **34:** 6054–9.

14. Frohne D. Untersuchungen zur Frage der Harndesinfizierenden Wirkungen von Barentraubenblatt-Extrakten. *Planta Med* 1970; **18:** 23–5.

15. Natural drugs with glycosides. In: Stahl E, editor. Drug Analysis in Chromatography and Microscopy. Ann Arbor: Ann Arbor Scientific Publishers, 1973: 97.

6.3 Discussion

6.3.1 Identification of Herbal Remedies and Herbal Ingredients

One of the objectives of the present research was to identify European herbal remedies available in the UK, primarily those being sold through pharmacies. This was not an easy task because despite the increasing range of herbal products available to the public, there is no comprehensive listing of all products.

The identified manufacturers ranged from small companies with just one herbal product, to larger more well established manufacturers with many products such as Booker Health, English Grains, Gerard House, Larkhall, and Potters. Some of the product ranges originated from outside the UK, such as those marketed by Arkopharma and Blackmores. The large number of products noted for Booker Health was due to three separate herbal ranges marketed under different trade names. The majority of the products either did not hold a product licence and were marketed as food supplements, or held a product licence of right (PLR) indicating their imminent review by the Department of Health. The review of products holding a PLR was completed in May 1990.

The majority of manufacturer replies only provided price lists and catalogues and did not detail the herbal ingredients contained in each product. It was therefore necessary to visit a number of pharmacies and healthfood stores to obtain accurate details on the herbal ingredients of herbal products stocked. It was recognised that whilst the identified manufacturers and their herbal products did not represent a definitive (e.g. geographically biased) nor static list, they provided a good indication of the type of European herbal ingredients available in herbal products on sale through pharmacies and healthfood stores in the UK. The lack of response from pharmacists regarding the type of herbal products stocked and the nature of herbal enquiries received was surprising. From the pharmacies visited it was evident that a wide variety of herbal products are stocked, and from the enquiries identified at the Welsh Drug Information Centre it was clear that pharmacists are being asked questions about herbal medicines.

Of the 200 stated herbal ingredients, some represented the same herb due to a variety of common names used. A league table was drawn up with preference given to those herbal ingredients present in the most products. In addition, herbs of particular current interest, such as ginkgo, were also given preference. In total, 141 herbal ingredients were selected for further information collation.

Another objective of the current research was to collate relevant data pertaining to the quality, safety and efficacy of European herbal remedies. Early on in the research it was decided to collate information on individual herbal ingredients rather than on specific herbal products. This decision was made in view of the difficulty encountered in obtaining data for individual products, the rapidly changing number and formulation of herbal products (primarily due to the Review on Herbal Medicine, see Chapter 2), and the large number of unlicensed herbal products.

6.3.2 Information Sources On Herbal Remedies

A variety of information sources were utilised to retrieve relevant phytochemical, pharmacological and toxicity information on the identified herbal ingredients. Pharmacopoeias such as the British Herbal Pharmacopoeia (BHP), the British Pharmaceutical Codex (BPC), the European Pharmacopoeia (Ph.Eur.), and Martindale provided a starting point for information retrieval. Many herbs are known by a variety of both Latin and common names and pharmacopoeias provided useful information on such terminology. In particular the 1934 BPC was referred to extensively since many herbs were deleted from the subsequent 1949 and 1954 editions.

A variety of core reference sources (Table 6.1) were utilised. Scientific sources provided references and often covered specific aspects of information on herbs, such as constituents (e.g. Guenther, 1948-1952; Hoppe, 1981; Leung, 1980; Morelli, 1983; Evans, 1996; Wagner, 1983) or toxicity (e.g. DeSmet et al, 1992 & 1993; Frohne & Pfander, 1984; Leung, 1980; Mitchell & Rook, 1979). Whilst not as extensively

referenced, the non-scientific sources provided useful information on unusual uses, doses employed, and precautions for usage (although the rationale was not always provided). Referenced pharmacological information was difficult to obtain from the majority of sources, Leung (1980) being the exception. An Australian publication stated to be aimed at healthcare professionals (Hamon & Blackburn, 1985) was poorly referenced and rather brief on factual information.

A number of primary journals were identified (Table 6.1) for regular review. In view of the broad range of journals in which information on medicinal plants is published, it was difficult to draw up a definitive core list of journals for regular screening. Different journals yielded different types of information such as clinically-orientated (e.g. British Medical Journal, Lancet), pharmacology (e.g. British Journal of Pharmacology, European Journal of Pharmacology, Human Toxicology and Journal of Pharmacy and Pharmacology), and phytochemistry (e.g. Journal of Ethnopharmacology, Journal of Natural Products (Lloydia), Planta Medica, and Phytochemistry). Subscriptions were made to the Journal of Alternative Medicine, and to Herbalgram and The Lawrence Review of Natural Products (two American publications).

In view of the wide range of primary journals in which papers on medicinal herbs were published, various secondary abstracting and indexing (A&I) services were utilised, namely Current Advances in Plant Science (CAPS), International Pharmaceutical Abstracts (IPA), Index Medicus, Chemical Abstracts, Medicinal and Aromatic Plant Abstracts, and Current Contents Life Sciences (CCLS). The use of IPA was abandoned in view of the long lag time for indexed articles. CCLS was reviewed weekly for a wide range of primary journals. The main limitation with CCLS was that screening was based on known journals of interest. CAPS was found to be a particularly useful A&I service since it contained a general section on Ethnobotany and another section on Secondary Products with sub-headings such as Alkaloids, Flavonoids and Terpenoids. Subject areas could therefore be scanned rather than specific journals.

On-line databases were the only feasible option to perform comprehensive retrospective searches for individual medicinal herbs. In particular, publications discussing

pharmacology (animal and human) and toxicology were required. Four bibliographic files were considered with the host Datastar which used a relatively simple search language. After some trial searches, Biological Abstracts and Chemical Abstracts were not used in view of their heavy bias towards phytochemistry, enzyme studies in plants, and agricultural research. Excerpta Medica (EM) and Medline (ML) yielded more pharmacologically/clinically-orientated papers and despite their slight overlap, both databases were searched.

EM and ML are not indexed with the view to retrieving clinically-orientated information for plant names. The two main difficulties encountered when searching EM and ML were deciding on appropriate search descriptors and choosing relevant papers for printing. On-line searching is extremely expensive (at the time that this research was undertaken, CD-ROM searching was not available at The School of Pharmacy library), with charges made for connection time and for the number of references printed. Considerable emphasis was placed, therefore, on increasing the search efficiency:-

Descriptors A minority of plant names were listed in the ML thesaurus thus ensuring a consistency of indexing. However, for the majority of plant names a free-text search using all possible synonyms was the only method of searching. This latter method can be considerably time consuming if not planned in advance of on-line connection. As a result of the free-text searching used, a number of "false drops" were obtained where the specified search term appeared in a different context.

Relevant Papers When searches yielded a high number of matches (common if searching performed using a variety of synonyms), it was necessary to limit the number of publication references for printing. Various approaches were used including:-

- print out title only (no charge) for review off-line
- limit by publication year (s)
- limit to studies in animals and/or humans
- limit to studies on adverse effects, poisoning, toxicology
- identify key descriptors used for a few references of known interest

The other main limiting factor of on-line databases for retrospective information retrieval is the date of the first indexed reference. The majority of databases are relatively young covering publication dates from, at the earliest, the mid-1960's (1966 for ML) or early 1970's (1974 for EM). Published work prior to these starting points will not be retrieved from the databases.

6.3.3 Information Needs of the Pharmacist

Herbal medicine is being increasingly used by the general public on a self-selecting basis to either replace or complement conventional medicines (Newall et al, 1996). Pharmacists may be faced with queries regarding herbal products either stocked in their own pharmacy or purchased from other retail outlets such as healthfood stores or supermarkets.

An objective of the current research was to determine the information needs of the pharmacist with respect to his/her role in the sale or supply of European herbal remedies. The traditional sources of product/drug information (e.g. British National Formulary, Martindale, Data Sheet Compendium, British Pharmaceutical Codex, Monthly Index of Medicines) utilised by pharmacists provide limited information on herbal products or their herbal ingredients. An analysis of enquiries received during 1986 by the Welsh Drug Information Centre (WDIC) at Cardiff Heath Hospital, which holds the specialist file on alternative medicine, indicated the need for clinically-orientated information on herbal remedies (Baldwin et al, 1987c). The three most popular herbs with respect to number of enquiries received were evening primrose, feverfew, and ginkgo. All three were subject to considerable media interest during 1986, highlighting the influence of the media over consumer interest.

It was clear from the results of the survey that pharmacists required clinically-orientated information on herbal products in an easily accessible format. In view of this, a datasheet layout was considered the most appropriate manner in which to present

information on herbal remedies. It was decided more relevant to produce a datasheet-style monograph for the 141 selected herbal ingredients, rather than for individual herbal products, for a number of reasons:-

- considerable flux in both the number and formulation of herbal products primarily, for licensed products, as an outcome of the Department of Health's Review on Herbal Medicine (see Chapter 2)
- the difficulty encountered in obtaining accurate details on herbal product constituents
- regional variation in some product availability.

The categories of information which it was decided to include in the herbal monographs are listed in Table 6.7. It was considered important to present the collated information in a clinically-orientated format that would be familiar to pharmacists. Therefore headings such as legal category, dose, pharmacological actions, side-effects and toxicity, and contra-indications and warnings were used. In addition, it was felt necessary to start each monograph with clear information on the specific herb being discussed, providing both Latin and common names, together with the plant part used. It was also considered useful for an indication to be given of pharmacopoeial entries for the herb together with its food use (if any). Provision of an evaluative summary for each herb, termed Pharmaceutical Comment, together with a list of specific references cited within the body of the monograph, were felt important and were included at the end of each monograph.

An objective of the current research was to establish a core reference source to meet the needs of the pharmacist with respect to European herbal remedies. Considerable thought was given to the type of information required, in addition to the 141 herbal monographs, to produce such a reference source. It was decided to exclude information on the identification of a herbal ingredient and on chemical structures of important constituents. Whilst this information is important to readers with a specialist interest in medicinal plants, it was felt to be inappropriate for the majority of pharmacists at which the reference source was aimed. Furthermore, whilst pictures of the included herbal ingredients would have made an attractive addition, they would have also considerably

increased the cost of the book perhaps making it prohibitively expensive to some pharmacists.

There are many issues specific to herbal remedies that affect their licensing and suitable use as medicines. It was considered important for the reader of the book to appreciate these issues and therefore an introductory chapter was written. This chapter provides an historical account of UK medicines legislation on herbal remedies and explains the current status of herbal remedies within European legislation. In addition, the chapter discusses issues specifically affecting the quality, safety and efficacy of herbal remedies. A number of tables and appendixes were drawn up to accompany the introductory chapter detailing, for example, potential drug/herb interactions, herbs best avoided during pregnancy, and herbs with specific pharmacological actions and constituent types.

Whilst the needs of pharmacists were central to the information included in the book, it was also felt that many other healthcare professionals would find its content useful and therefore this was reflected in the title. "Herbal Medicines - A Guide for Healthcare Professionals" was published by the Pharmaceutical Press in January 1996 (Newall et al, 1996).

7. CONCLUSIONS AND RECOMMENDATIONS

7.1 Legislation of Herbal Remedies

The effective regulation of herbal remedies as medicines is a grey area within UK medicines legislation. Herbal remedies are specifically referred to in the Medicines Act (MA) (Anon, 1968) and subsequent legislation, with exemptions from licensing requirements permitted for remedies complying with sections 12 and 56 (see Chapter 2). These exemptions were aimed at remedies prepared by a medical herbalist and at remedies consisting merely of dried crushed or comminuted herbal material with no medicinal claims made on the labelling. In practice, a vast number of formulated herbal remedies have been able to avoid licensing as a medicine by simply omitting medicinal claims from their labelling and by being marketed as dietary supplements (DSs). In the late 1980's a review of licensed herbal remedies carried out by the Medicines Control Agency (MCA), to comply with European Community (EC) Directives 65/65 (Anon, 1965) and 75/319 (Anon, 1975), rationalised the number and nature of herbal ingredients, assessed their quality and safety, and reviewed medicinal claims. This review did not, however, consider the plethora of unlicensed herbal remedies which continued to be available in the UK.

In January 1995 new UK regulations took effect (Anon 1994a) which implemented EC medicines legislation into UK law. The main impact of this new legislation for herbal remedies was in the definition of a medicinal product, which now stated that a product could be considered medicinal by virtue of its presentation or function. If acted upon, this new definition would have had a major impact on the many unlicensed herbal remedies either exempted by the MA or marketed as a DS. Not surprisingly, considerable pressure was lobbied at the government by the British Herbal Medicine Association (BHMA) over these impending changes. A solution was found by referring to the phrase "industrially produced" used in the EC definition of a medicinal product.

Thus SI 3144 (Anon, 1994a) states that a herbal remedy is not industrially produced if it complies with the existing exemptions for herbal remedies under the MA, thus maintaining the status quo. "Industrially produced" is not defined anywhere in SI 3144.

In line with the EC definition of a medicinal product, the Medicines Act Leaflet 8 (MAL 8) (Anon, 1995d) clearly sets out the factors taken into consideration by the MCA in determining whether a product is a medicine (i.e. both presentation and function). However, MAL 8 also states that it does not affect the current legal status of certain products including exempted herbal remedies and DSs. Not surprisingly, the government has for the meantime avoided addressing the difficult issue of whether to license formulated herbal products containing herbal ingredients that are primarily medicinal by function, but which omit medicinal claims from their labelling. The use of such DSs as medicines was highlighted by the recent Consumers' Association policy report (Anon, 1996r), which stated that of the people surveyed more considered DSs to be medicines rather than foods. It seems nonsensical that a consumer may be faced with similar herbal products on adjacent display, which only differ by their licensed status. In addition to any concerns over quality and safety, unlicensed herbal products are not permitted to include details of their intended medicinal uses on the labelling. These uses may be well established for the herbal ingredients in the product but nevertheless cannot be passed onto the consumer. Clearly, it would seem appropriate for there to be some form of licensing system for all herbal remedies to remove the current dual standard that exists within the UK.

For the many herbal products that are neither licensed medicines nor considered to be foods, there is no definite government body with accountability for these preparations. Unlicensed DSs that are considered foods fall under the remit of the Food Safety Act 1990 although, unlike medicines, DSs rarely undergo a pre-market safety review. The onus is on the manufacturer to use due diligence to avoid committing an offence. DSs may undergo a safety review by the Advisory Committee on Novel Foods and Processes (ACNFP) if they contain novel foods, i.e. those not previously consumed in significant quantities in the UK. Such a review is anticipated to become statutory under future EC legislation (Anon, 1996r). DSs may also be reviewed by other government

committees if there is any cause for concern, but this process is essentially on an ad-hoc basis. Food supplements containing comfrey, for example, were voluntarily withdrawn by the health food trade following recommendations made to the Food Advisory Committee and to the Ministry of Agriculture, Fisheries and Foods (MAFF) by the Committee on Chemicals in Food (Newall et al, 1996). The recent move by the MCA to assume responsibility for the monitoring of side-effects associated with unlicensed herbal remedies (Anon, 1996p) may signal a welcome change to this current confusion over accountability. A recent study of DSs in the South East of England (SEMCOT) highlighted the problem of accountability (Anon, 1996r). The study reportedly identified 147 DSs considered to be making illegal medicinal claims. Subsequent review of these products by the MCA categorised them either as unlicensed medicinal products on the basis of their presentation, or as foods making illegal claims.

The BHMA has recognised that in order to preserve the freedom allowed for herbal medicines under exemptions specified in the MA, self-regulation is required in order to maintain high standards within the industry and to expose and eradicate poor practices. To this end, and in consultation with the MCA, a Code of Practice has been proposed by the BHMA to all its members, which is intended to receive final endorsement early in 1997 and become fully operational from January 1999 (Perfitt, 1996). The stated objective of the Code is to "promote the safety, quality and efficacy of unlicensed herbal remedies by prescribing a clear framework of Good Practice within the UK and EC legislation with the object of protecting the health and well being of the patient/customer when choosing an unlicensed herbal remedy". The proposed Code addresses the following areas: raw materials, manufacture, labelling and quality/adverse reactions, and proposes compliance with existing medicines legislation such as the General Sales List, the Herbal Remedies Order 1977, and the Guide to Good Manufacturing Practice. The Code also lists reference sources to be used in establishing the quality of a raw material (European Pharmacopoeia, British Pharmacopoeia, British Herbal Pharmacopoeia, Chinese Pharmacopoeia), and substances prohibited from unlicensed products (heavy metals, synthetic medicinal substances, substances derived from endangered animal species).

Whilst the proposed BHMA Code of Practice is a welcome step towards ensuring the standards of unlicensed herbal products, it will still be voluntary and must be suitably enforced to be effective. In addition, it will obviously only apply to BHMA members. This will lead to the rather fragmented situation with respect to herbal remedies in the UK of licensed products, unlicensed but manufactured by BHMA members, and other unlicensed herbal products. One has to wonder whether the incentive to licence a herbal preparation will be reduced if, in time, products complying with the BHMA Code gain general acceptance over their quality, safety and efficacy (after all, the intended purpose of the Code). Essentially, manufacturers of licensed herbal products will be paying a considerable licensing fee for the privilege of stating medicinal claims on their labelling.

The new marketing authorisation (MA) systems within the EC seek to promote the free movement of medicinal products from one member state (MS) of the EC to another, by applying uniform authorisation rules to all MSs. Herbal remedies would be authorised via the mutual recognition (MR) procedure. However, it is difficult in reality to envisage this system operating successfully for herbal remedies when so many differences continue to exist between MSs over the interpretation and implementation of EC legislation into their national law. Cultural traditions with respect to herbal remedies vary considerably between MSs and differences exist over individual MS interpretation of EC requirements for proof of quality, safety, and efficacy. Until fundamental principles such as the information required for satisfactory identification of a plant source (including mutually recognised sources such as the European Pharmacopoeia) or for proof of efficacy (e.g. principle of "traditional" use, traditional use in one MS may not be acceptable in another) are agreed, the MR procedure will not be practical for herbal remedies.

7.2 Quality of Herbal Remedies

As with all medicines, a herbal remedy should be of a suitable quality and the many factors that need to be considered in ensuring the quality of herbal remedies were discussed in Chapter 3. Rigorous authentication of the starting material, essential for all medicines, presents particular difficulties when herbal remedies are considered. Rather than well-defined chemical entities, the starting materials for herbal products are vegetable drugs each representing a complex mixture of chemical constituents. There are many natural factors which may affect the quality of a vegetable drug that simply do not need to be taken into account for synthetic drugs. Factors such as correct botanical identification, adulteration and contamination all need to be considered. The special requirements of herbal products with respect to quality have been recognised at an EC level, and guidelines on the quality and manufacture of herbal remedies (Anon, 1989c; Anon, 1992b) provide advice on the nature of information that should be provided by manufacturers to ensure the quality of their herbal products. However, in practice, some of the desired information (such as growing conditions, time of harvesting) may not be available. In addition, for many of the identified quality control factors (such as microbial contamination, pesticide and fumigant residues) EC legislation does not set specific limits, thus leaving room for MS interpretation.

Quality control procedures should ensure the reproducible quality of a herbal product. In view of the chemically heterogeneous nature of each herbal ingredient, intermediate and finished product specifications are vital to ensuring the quality of the product. Designing suitable analytical procedures (quantitative or qualitative) to ensure the quality of not just starting materials, but also intermediate and finished products, presents a number of difficulties for herbal remedies. Even if active constituents in each herbal ingredient are known, analyses cannot be based solely on the presence of these constituents, since it is the total chemical makeup of the product that is important. This situation is further complicated in multi-ingredient preparations containing two or more herbs. The responsibility lies with a manufacturer to justify the suitability of analytical procedures and specifications used in the manufacture of their product. A licensed product will have been assessed by the MCA which is therefore in a position not only to ensure batch to batch consistency, but also inter-manufacturer uniformity to specification data permitted for similar starting materials and finished products.

Unlicensed products do not offer such an opportunity for assessment of their quality. The proposed BHMA Code (see 7.1) will hopefully provide the assurance needed over the quality of unlicensed herbal products manufactured by BHMA members. How comparable quality standards accepted within the Code will be with MCA judgements in situations where there are no clear specifications, will be an important factor in the future application of the Code.

Ensuring the quality of a herbal product obviously involves the principle of good manufacturing practice. Quality problems with a medicine may come to light after a defect or safety report. It is important that, as for all medicines, the manufacturer of a herbal product is in a position to swiftly assist with any potential quality problems by providing details such as batch numbers, formulation details, and any recent changes to the manufacturing process, and be in a position to recall affected products if necessary.

EC guidelines on the quality and manufacture of herbal remedies (Anon, 1989c; Anon, 1992b) aimed to remove differences between MSs in their interpretation of the relevant EC directives. In practice, however, there remain many difficulties in achieving harmonisation over the quality requirements of herbal remedies. Rigorous authentication of the starting material is recognised as essential in ensuring the quality of a herbal remedy. The key difficulty within the EC is in agreeing on a common definition for herbal starting materials. Few herbal drugs are included in the European Pharmacopoeia (Anon, 1997a) and until comparable specifications are accepted for herbal starting materials, comparisons of different products utilising the same botanical source(s) will not be feasible. The small number of ESCOP (European Scientific Co-operative on Phytotherapy) monographs accepted by the CPMP (Committee for Proprietary Medicinal Products) highlights the difficulty in achieving EC definitions of herbal drugs. Harmonisation of herbal preparations (fluid extract, tincture) presents even greater difficulties. National pharmacopoeial monographs for herbal drugs often contain varying details of fluid extract and tincture preparations. In addition to these national differences in specification details, it is recognised that their use in industrially prepared herbal preparations is limited (Keller, 1994). If specifications for the starting

materials cannot be agreed upon, achieving a Summary of Product Characteristics (SPC) for a herbal remedy will be virtually impossible.

Control over the quality of unlicensed herbal products imported into the UK is extremely difficult to maintain. National differences over the permitted use of certain herbs may result in a herb considered unsuitable for use in the UK nevertheless being available in imported products. Shaw et al (1996) highlighted this problem with reference to chaparral and Ma Huang (*Ephedra sinica*), whose use in the UK is either not permitted or restricted, respectively. No such restrictions apply in the US and therefore imported American products may well contain these herbal ingredients. The Department of Health can request the importing company to remove any products found to contain unsuitable herbal ingredients from sale in the UK (Shaw et al, 1996), but identification of the product in the first place is a difficult task and essentially ad-hoc.

Although outside the scope of this thesis, it is pertinent to comment on the many "traditional" Chinese and Asian herbal medicines that are increasingly available in the UK. Numerous instances of adulteration with conventional medicines or toxic metals have been documented for these preparations (see Chapter 3), usually only coming to light after precipitating a safety issue. It is difficult to envisage how any legislation could remove these products from UK sale, and efforts are therefore probably best directed in educating both health professionals and the public as to the dangers associated with their use.

7.3 Safety of Herbal Remedies

Concerns over the safety of herbal remedies have existed for many years and have been discussed in many publications discussing adverse reactions (e.g. Buurma et al, 1983; Buurma & Vulto, 1984; D'Arcy, 1991; DeSmet, 1992 & 1995; DeSmet et al, 1992 & 1993; Dukes, 1977, 1980, 1994; Penn, 1981, 1982; Saxena, 1985). A herbal remedy may present either a direct or indirect health risk. Direct risks may be due to the

inherently toxic nature of the herbal ingredient(s) or because of poor quality resulting in adulteration or contamination with toxic substances. The impact of poor quality on the safety of herbal remedies has been discussed in Chapter 3 and under 7.2. Indirect risks may result from the use of an ineffective remedy delaying, interfering with, or replacing conventional effective treatment. In addition, consumer-related parameters such as age, genetics, concomitant disease and/or drug therapy may affect the likelihood of a herbal remedy causing an adverse reaction (DeSmet, 1995). Inherently toxic herbs and the potential for interaction of herbal ingredients with therapeutic patient groups or drug therapy have been discussed in detail in Chapter 4.

The extensive traditional use of plants as medicines has enabled those with acute and obvious signs of toxicity to be well recognised and their use avoided. Medicines legislation can effectively protect the general public from herbs or herbal constituents considered to represent a specific hazard, with respect to their pharmacological potency or potential toxicity. For instance, a number of pharmacologically potent plants are classified as Prescription Only Medicines (POM), cyanogenetic glycoside-containing products are restricted, and the General Sales List may limit the route or amount of herb permitted for medicinal use. Most recently, several *Aristolochia* species have been assigned POM status, in view of the recent cases of renal toxicity in Belgian associated with slimming preparations which contained *Aristolochia fangchi* (Anon, 1997b; Cosyns et al, 1994; Vanhaelen et al, 1994).

However, the premise that traditional use of a plant for perhaps many hundreds of years establishes its safety does not necessarily hold true. The more subtle and chronic forms of toxicity, such as carcinogenicity, mutagenicity, and hepatotoxicity, may well have been overlooked by previous generations and it is these types of toxicities that are of most concern when assessing the safety of herbal remedies. Recent reports of hepatotoxic reactions associated with chaparral (Anon 1992a & 1993a; Clark & Reed, 1992; Gordon et al, 1995; Katz & Saibil, 1990) and germander (Larrey et al, 1992; Mostefa-Kara et al, 1992), both plants with a traditional use as herbal remedies, highlight this concern.

All medicines are assessed for the occurrence of adverse reactions in pre-licensing trials. The detection ability of such trials is primarily restricted by the population size exposed to the medicine. It is been suggested that the number of studied patients must be three times greater than the frequency of the adverse reaction to enable a 95% chance of observing the reaction in the studied population (DeSmet, 1995). Consequently, in order to detect rare adverse reactions post-licensing monitoring of spontaneous adverse reactions is essential for all medicines throughout their lifetime. In addition, it is important for a serious and unusual reaction to a drug in one country to be rapidly communicated to licensing authorities in all other countries in which the drug is used. Similarly, it is important for there to be good communication between individual organisations concerned with the monitoring of adverse reaction data to phytomedicines. DeSmet (1995) highlighted the need for a pooling and subsequent dissemination of known information regarding the toxicity of herbal drugs. Recent reports by the Medical Toxicology Unit (MTU) at Guy's Hospital (Shaw et al, 1996) and the Consumers Association (Anon 1996r) have identified a need for an effective mechanism for reporting and monitoring adverse reactions to herbal remedies and DSs. It is therefore encouraging to see the pharmacovigilance of phytomedicines discussed within an international forum (Anon, 1996n; Barnes, 1997), and the piloting of an on-line "yellow-card" scheme, called Phytonet, accessible via the Internet. Phytonet is part of an EC-sponsored three-year project (BIOMED) which aims to determine EC standards for the safe and effective use of phytomedicines (Barnes, 1997). Importantly Phytonet has been developed in association with other centres concerned with the collection of adverse reaction data to phytomedicines, namely the World Health Organisation (WHO) in Uppsala, Sweden, the MTU in London, and the Royal Dutch Association for the Advancement of Pharmacy in the Hague.

In the UK, licensed herbal remedies come under the existing yellow card spontaneous adverse reaction reporting scheme for medicines. Until recently, there has been no clear mechanism for health professionals to report suspected adverse reactions to unlicensed herbal remedies. However, in response to the MTU report (Shaw et al, 1996), the MCA has announced an extension of the yellow card system to unlicensed herbal products (Anon, 1996p). This is a welcome move in view of the large number of unlicensed

herbal remedies legally available in the UK and, in addition, may prompt reports to be submitted on imported traditional remedies that pose a possible health risk. In addition to the reporting of adverse reactions by health professionals, it is important for manufacturers of herbal preparations to also assume some responsibility for communicating reports of adverse reactions to the licensing authority. The undertaking by the BHMA, as part of its proposed Code of Practice, to inform the MCA of any safety or defect issues is therefore an important development within the UK.

Initiatives that have taken place within the EC with respect to the pharmacovigilance of phytomedicines are an important step forward. Ultimately, pharmacovigilance is only truly effective if carried out for all exposed population groups. The tremendous increase in the use of phytomedicines within the EC makes it essential for there to be an EC-wide reporting system. Hopefully, the Phytonet system will provide a suitable platform on which to develop such a system. EC-wide communication of adverse reactions to licensed medicines already exists. It would seem inappropriate for a separate communication system to be developed specifically for unlicensed remedies. Hopefully, if other MS licensing authorities assume a similar position to the MCA regarding adverse reactions to unlicensed herbal remedies, then use can be made of existing communication channels. Whether or not the European Medicines Evaluation Agency (EMEA) will eventually assume a co-ordinating role for the pharmacovigilance of phytomedicines will be interesting to observe. Since many herbal products are imported into the EC it is also important for there to be a good awareness of any phytomedicine-related safety issues occurring outside the EC. The link between the Phytonet project and the WHO centre, for instance, is particularly important in this respect.

7.4 Efficacy of Herbal Remedies

It is clear that plants offer a wealth of pharmacologically active constituents and potentially clinically beneficial compounds. Reports from recent international symposia have highlighted the continuing interest in the value of medicinal plants, with speakers

referring to the use of St. John's wort in depression, mistletoe lectins in anti-cancer therapy, valerian as a sedative, and hawthorn in heart failure (Anon, 1996g-ml; Anon1996o). However, the majority of herbal remedies currently available in the UK are either unlicensed (and therefore make no medicinal claims), or remain limited to licensed indications based on "traditional" uses in minor, self-limiting conditions. Whether or not herbal preparations licensed for "traditional" uses contain sufficient amounts of the herbal ingredient(s) to be effective remains debatable. Indeed, the doses permitted are usually far smaller than those stated in herbal pharmacopoeias. It is highly unlikely that herbal manufacturers will incur the costs of performing clinical trials to establish the efficacy of a preparation used in a minor, self-limiting condition, especially when this is not a licensing requirement. This situation, however, is not totally at odds with the many non-herbal over-the-counter remedies that are based on traditional recipes and not on the results of clinical trials.

It is important for herbal medicines to progress beyond the minor ailment category and to be considered as suitable alternatives to conventional drugs. However, this will only become reality if pharmaceutical manufacturers are prepared to invest in the clinical development of herbal medicines as with other medicines. Positively, this does seem to be happening as more well-established pharmaceutical manufacturers acquire plant-based research companies (Anon, 1996f). However it is important that the emphasis of future pharmaceutical development is not placed totally on isolating individual chemical entities, and that the tradition of utilising whole plant extracts is maintained. Factors affecting the clinical trial development of herbal remedies, namely funding, chemical complexity and suitable entry criteria/endpoints, have been discussed in Chapter 5.

One of the key difficulties associated with establishing the efficacy of a herbal remedy is in formulating a preparation of reproducible quality, such that bioequivalence can be demonstrated between different batches. Establishing bioequivalence is essential if the use of whole plant extracts, as opposed to isolated constituents, is to be successfully developed. Comparison of documented clinical trials for a herbal drug is often hampered by the non-bioequivalent nature of preparations used in the different trials.

Furthermore, when considering the free movement of medicines within the EC, bioequivalence between preparations manufactured in different MSs is paramount. However, until current differences between MSs on issues such as definition of starting materials and quality control limits are resolved, it is difficult to envisage the circulation of "generic" herbal preparations within the EC. At a time when pharmaceutical manufacturers are looking to license their medicinal products in as many MSs as possible via one application, difficulties encountered over the harmonisation of licensing requirements for herbal remedies may well hamper their development. Manufacturers will need to produce licence applications tailored to the needs of each MS, the very opposite to the intended aim of the EC licensing system.

Unsubstantiated medicinal claims have long tarnished the image of herbal remedies. Licensed remedies may only refer to their licensed indications. Unlicensed herbal remedies are often marketed as DSs and therefore legislation covering claims made for foods is relevant. DSs are covered by the general provisions laid down by the Food Safety Act 1990, and must comply with the Food Labelling Regulations 1996 which prohibit an explicit or implied claim, in labelling or advertising, that a food is "capable of preventing, treating or curing human disease" (Anon, 1996r). DSs often utilise suggestive product names and imagery on packaging to imply a particular activity. The recent Consumers' Association report stated that suggestive product names do imply a medicinal benefit to consumers (Anon, 1996r). In addition, unlicensed preparations often make use of associated literature placed adjacent to the sales display to imply various medical uses. Furthermore, there are numerous books available discussing the medicinal uses of individual herbs which consumers can use to deduce their own opinions on the intended uses of unlicensed herbal remedies. There is no law to prevent the publication of these books which may refer to known potentially toxic herbs with no cautionary statement, and include recommendations for medical uses that are clearly unsuitable for self-treatment. A recent publication entitled "The Complete Illustrated Holistic Herbal" (Hoffman, 1996) illustrates this concern. It includes references to the use of broom (cardiotoxic), Lily of the Valley (cardioactive), and ragwort (hepatotoxic), and includes recommendations for the self-treatment of numerous conditions including pleurisy, whooping cough, and infections of the middle ear and

eyes. Whilst such publications may provide the reader with much interesting information, the untrained eye will not be able to distinguish between harmless and harmful advice.

In addition to the Food Safety Act, Codes of Practice exist covering the labelling and claims made for DSs. The Proprietary Association of Great Britain (PAGB) has a code on Advertising Claims for Food Supplements, and the Health Food Manufacturers Association (HFMA) has a Code of Advertising Practice. In view of the examples of suggestive product names and imagery identified by the Consumers' Association report (Anon, 1996r), and the many DSs considered to be making illegal medicinal claims in the SEMCOT study (Anon, 1996r), one has to question the effectiveness of these voluntary codes. The British Code of Advertising Practice administered by the Advertising Standards Authority (ASA) covers printed adverts. The ASA recently upheld a complaint by the PAGB regarding medicinal claims made for an unlicensed ginkgo product (Anon, 1996q). Enforcement of legislation (voluntary or statutory) regarding health claims and advertising is expensive and time consuming, and it is difficult to ensure total compliance. Efforts may be better placed in assisting those organisations committed to maintaining rigorous and ethical standards within the health supplements sector, and educating the public as to the potential dangers associated with certain types of products.

An unlicensed product is not permitted to include details of its intended medicinal uses on the labelling, even if the uses are well established. The Consumers' Association report (Anon, 1996r) highlighted this problem by reference to folic acid. The benefits of folic acid supplementation against neural tube defects are well recognised, but only folic acid products licensed as a medicine can make reference to this established fact (Anon, 1996r). There are many unlicensed herbal remedies on sale to the public whose labelling therefore provides no information on suitable medicinal uses. Consumers may well be confused when faced with licensed and unlicensed herbal products that appear side-by-side on the shelf.

7.5 Pharmacy Involvement with Herbal Remedies

Many pharmacies now stock herbal products which reportedly account for 50% of over-the-counter purchased complementary medicines (Platt, 1996). Clearly pharmacists are becoming increasingly involved in the sale and supply of herbal products and therefore have a professional duty to be able to provide factual advice on these products, irrespective of personal beliefs. Recent correspondence from pharmacists has both supported (Finberg, 1996; Madge, 1996) and refuted (Tidy, 1996) this professional responsibility. However, if pharmacists wish to capitalise on the business opportunity offered by the sale of herbal remedies, they should also be prepared to advise the consumer on their suitable use as medicines. If not, there is nothing to distinguish a pharmacy from a health food outlet with respect to the sale of herbal products. Two courses are now available for individuals to formally train in herbal medicine. One is run by the National Institute of Medical Herbalists whilst the other is an Honours degree course at Middlesex University. If pharmacists are not prepared to take on the challenge of advising on the suitable use of herbal remedies, there will soon be non-pharmacists in a position to do so. This could result in non-pharmacy retail outlets being able to provide advice of a superior quality to that obtained from pharmacies. As the consumers' definition of a medicine widens to include products such as herbal remedies, pharmacists need to decide whether they wish to remain the experts on providing advice on the use of all medicines. From present trends, it is likely that both the choice and use of non-allopathic medicinal preparations will continue to increase and as a profession, pharmacy needs to be able to provide advice on such preparations. The recent Consumers' Association report on DSs (Anon, 1996r) reported the following statistics on sources used by consumers who wished to ascertain additional information on DSs: doctor 32%, book 27%, chemist 21%, health food shop 21%. It is worrying that more people would read a book than ask a pharmacist, and that the same number of people would visit a health food shop for advice as a pharmacy.

The key to enabling pharmacists to advise on the suitable use of herbal remedies is education and information. Suitable modules should be included in pharmacy under-graduate courses. In addition, and perhaps of greater importance, reliable and easily

accessible reference sources on herbal remedies need to be available to the pharmacist. The usual reference sources used by pharmacists to obtain information on a particular medicine, such as the British National Formulary, ABPI Datasheet Compendium and Martindale, contain either no or little reference to herbal medicines. Since the early 1980's, many articles on herbal remedies have been published in the Pharmaceutical Journal. Whilst of interest to the specialist reader, both the length and style of many of the articles may discourage pharmacists with no specific interest in herbal remedies from reading further. In addition, journal articles do not easily offer a permanent reference source. The importance of enabling pharmacists to extend their provision of professional advice to herbal remedies was recognised some years ago in the Netherlands by the pharmacists' professional body (Royal Dutch Association for Advancement of Pharmacy), which provided pharmacists with pharmacist-orientated and patient-orientated information on herbal remedies (DeSmet, 1989). A one day symposium held in March 1997 at the Royal Pharmaceutical Society headquarters, entitled "Are natural therapies safe and effective?", hopefully signals a demand and recognition for pharmacist education in this area.

In addition to being able to provide advice on the suitable use of herbal remedies, pharmacists need to be able to identify those products unsuitable for use and which should not be available for purchase in a pharmacy. Pharmacist awareness of quality and safety issues for herbal remedies is essential, and developing a means of communicating such information to pharmacists in a permanent and regularly updated format is key. It is similarly important that pharmacists appreciate the difference between licensed and unlicensed herbal remedies with respect to the product's assurance over quality, safety and efficacy. Whilst it is unrealistic to suggest that pharmacies should only supply licensed herbal remedies (some popular remedies are only available as unlicensed products), awareness of Codes of Practice such as that proposed by the BHMA will be important in determining which unlicensed products are suitable to stock.

Unlicensed herbal remedies will not provide any information on their labelling as to their intended uses. With many popular remedies only available in an unlicensed form

and available for purchase in pharmacies, this places a responsibility on pharmacists to be able to advise on the use of such products which, even though unlicensed, may offer potentially useful treatments in specific therapeutic conditions. This category may include, for instance, feverfew, evening primrose, and ginkgo. In order to be able to fulfil this role, pharmacists need to be provided with concise information assessing the current scientific knowledge of a particular herb. For example, much has been documented in the scientific literature on ginkgo which in Germany, is a regularly prescribed medicine. In the UK there are currently no licensed ginkgo-containing products, although many unlicensed preparations are available together with pamphlets and books discussing the benefits of ginkgo. In general, the intended medicinal uses of ginkgo (e.g. treatment of cerebral and peripheral arterial insufficiency) are not suitable for self-diagnosis (Newall et al, 1996). However, most pharmacists would be unable to respond to consumer queries on the suitable use of ginkgo products and would not have an information source readily available from which to ascertain an answer.

7.6 Conclusions and Recommendations

The aim of the present research was to increase the pharmacist's awareness of the pharmacological properties of herbal ingredients in European herbal products.

The objectives of the research were to:

- Identify European herbal remedies available in the UK, primarily those being sold through pharmacies
- Consider the role of the pharmacist in the sale or supply of European herbal remedies
- Determine the information needs of the pharmacist to effectively perform this role
- Collate relevant data pertaining to the quality, safety and efficacy of European herbal remedies

- Establish a core reference source to meet the needs of the pharmacist with respect to European herbal remedies

Conclusions

The current research identified 200 herbal ingredients of European herbal remedies available through pharmacies and health food stores, of which 141 were selected for collation of information. In supplying these remedies, the pharmacist clearly needs to be able to provide professional advice on their suitable use as medicines. In order to effectively perform this role, the pharmacist needs access to a reliable reference source providing scientific information presented in a clinically-orientated format. In addition, the pharmacist needs to be aware of the legal status of herbal remedies as medicines, and be able to discern those unlicensed products which are unsuitable for use.

The major part of this thesis deals with the issues surrounding the use of herbal remedies as medicines, namely legislation, quality, safety and efficacy and is presented in Chapters 2 - 5. Chapter 1 provides a general introduction to the use of complementary therapies and Chapter 6 describes the methods used and results obtained in the current research.

A reference book entitled "Herbal Medicines - A Guide for Healthcare Professionals" (Newall et al, 1996) brings together the information collated for the 141 herbal ingredients as a series of datasheet-style monographs. In addition, the book provides an overview of the quality, safety and efficacy issues affecting herbal remedies, and an account of the current legal status of herbal remedies as medicines within the EC and the UK. The book also includes a number of appendixes providing information on potential interactions between herbal remedies and therapeutic patient/drug groups, and on herbal ingredients with specific pharmacological actions or constituent types. The book was published by the Pharmaceutical Press in January 1996.

Recommendations

- Herbal remedies should be regarded as medicines, and not merely dietary supplements, irrespective of their licensed status.

- Pharmacists should be prepared to provide professional advice on the use of herbal remedies as medicines, and be willing to attain a suitable level of knowledge in order to fulfil this requirement.

- Consideration should be given by the Royal Pharmaceutical Society of Great Britain to the provision of continuing education for pharmacists on herbal remedies.

- The reference source produced as a result of the current research should be readily available to pharmacists.

- Pharmacists need to be aware of any quality, safety or efficacy issues associated with herbal remedies, and should be able to identify those unlicensed products which are unsuitable for use.

- Consideration should be given by the Royal Pharmaceutical Society of Great Britain to the need for future updating of the reference source produced as a result of this research. In addition, the requirement for a similar reference source on non-European herbal remedies should be considered.

8. BIBLIOGRAPHY

Abdul-Ghani A-S, Amin R & Suleiman MS, 1987, Hypotensive effect of *Crataegus oxycantha*, Int.J.Crude Drug Res., 25, 216-220

Abel G, 1987, Chromosone damaging effect on human lymphocytes by β-asarone, Planta Medica 53, 251-3

Agrawal OP, Bharadwaj S & Mathur R, 1980, Antifertility effects of fruits of *Juniperus communis*, Planta Medica 40 (Suppl), 98-101

Ainsworth JBL, 1996, What I meant was..., Pharm.J., 257, 622

Akerele O, 1988, Medicinal plants and primary health care: an agenda for action, Fitoterapia, 57, 35-363

Albert-Puleo M, 1980, Fennel and anise as estrogenic agents, J.Ethnopharmacol., 2, 337-344

Amagaya S, Sugishita E & Ogihara Y, 1985, Separation and quantitative analysis of 18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid in *Glycyrrhiza radix* by gas-liquid chromatography, Journal of Chromatography, 320, 430-434

Amann W, 1966, Umkehrung der pharmakologischen wirkung von *Agnus castus* bei niedriger dosierung. (Gleichzeitig ein beitrag zur endokrinologie der sexualhormone)., Z.Forsch Praxis Fortbildung (Med), 7, 229-233

Amann W, 1975, Akne vulgaris und *Agnus castus* (Agnolyt^{R}), Z.Allg.Med., 51, 1645-1648

Amann W, 1979a, Pramenstruelle Wasserretention. Gunstige wirkung von *Agnus castus* (Agnolyt^{R}) auf pramenstruelle wasserretention, Z.Allg.Med., 55, 48-51

Amann W, 1979b, Das "pramenstruelle syndrom" hat viele gesichter. Haufig bringt schon die gezielte anamnese aufschluss, Arztl Praxis, 31, 3091-3092

Amann W, 1982, Amenorrhoe. Gunstige wirkung von *Agnus castus* (Agnolyt^{R}) auf amenorrhoe, Z.Allg.Med., 58, 228-231

Amann W, 1984, Ist die acne vulgaris eine psychosomatische erkrankung? Versuch einer klarung: Der psychosomatische aspekt der scne vulgaris, Artzliche Kosmetologie, 14, 162-170

Ammon HPT & Handel M, 1981a, Crataegus, toxicology and pharmacology. Part I: Toxicity, Planta Med., 43, 105-120

Ammon HPT & Handel M, 1981b, Crataegus, toxicology and pharmacology. Part II: Pharmacodynamics, Planta Med., 43, 209-239

Ammon HPT & Handel M, 1981c, Crataegus, toxicology and pharmacology. Part III: Pharmacodynamics and pharmacokinetics, Planta Med., 43, 313-322

Anderson E & Anderson P, 1986, Complementary medicine and the general practitioner, Br.Med.J., 293, 53

Anderson E & Anderson P, 1987, General practitioners and alternative medicine, J.Royal College of General Practitioners, 37, 52-55

Anderson LA, 1991, Personal communication

Anderson LA, 1993, Regulatory aspect of Herbal Medicines in the UK. (Proceedings of a lecture held at Stratford-Upon-Avon), European Phytotelegram, 5, 18-22

Anderson LA, 1997, Personal communication

Anderson LA & Phillipson JD, 1982, Mistletoe - the magic herb, Pharm.J., 229, 437-439

Anderson LA & Phillipson JD, 1985, Herbal medicine: education and the pharmacist, Pharm.J., 236, 303-5

Andersson KE & Johannsson M, 1973, Effects of viscotoxin on rabbit heart and aorta, and on frog skeletal muscle, Eur.J.Pharmacol., 23, 223-31

Anon, 1965, Council Directive 65/65/EEC, Off.J.EC., No.22, 20-24

Anon, 1968, The Medicines Act, London: HMSO

Anon, 1971, Statutory Instrument (SI) 1971: 1450, The Medicines (Exemption from Licences) (Special and Transitional Cases) Order, London: HMSO

Anon, 1973, British Pharmaceutical Codex, London: The Pharmaceutical Press

Anon, 1975, Council Directive 75/319/EEC, Off.J.EC, 18(147), 13-22

Anon, 1976, International Agency for Research in Cancer (IARC), IARC Monogr.Eval.Carcinog. Risk Chem. Man, 10, 265-342

Anon, 1977, Statutory Instrument (SI) 1977: 2130, The Medicines (Retail Sale or Supply of Herbal Remedies) Order, London: HMSO

Anon, 1978a, The promotion and development of traditional medicine (Technical Report Series 622), Geneva: World Health Organisation: HMSO

Anon, 1978b, The Medicines (Labelling and Advertising to the Public) Regulations 1978, London

Anon, 1979, Formulating strategies for Health for All by the year 2000, Geneva: World Health Organisation

Anon, 1981, Global strategy for Health for All by the year 2000, Geneva: World Health Organisation

Anon, 1982, Medicines Act Leaflet (MAL) 8. A Guide to the Status under the Medicines Act of Borderline Products for Human Use, London: DHSS Medicines Division

Anon, 1983a, Celestial Seasonings Recalls Comfrey Tea, Herbalgram, Fall/Winter, 2

Anon, 1983b, Statutory Instrument (SI) 1983: 1212, The Medicines (Products Other Than Veterinary Drugs) (Prescription Only) Order, London: HMSO

Anon, 1984a, Mislabelled Remedy Recalled, Herbalgram 1 , 5

Anon, 1984b, Statutory Instrument (SI) 1984: 769, The Medicines (Products Other Than Veterinary Drugs) (General Sales List) Order, 1984, as amended by SI 1985: 1540, SI 1987: 910, SI 1989: 969, SI 1990: 1129 and SI 1994: 2410, London: HMSO

Anon, 1984c, Statutory Instrument (SI) 1984: 187, The Medicines (Cyanogenetic Substances) Order, London: HMSO

Anon, 1985, Ginseng Age and Potency Correlated, Herbalgram, 2, 5

Anon, 1986a, Extract of *Ginkgo biloba* (Egb 761), Presse Med., 15, 1438-1598

Anon, 1986b, British Medical Association: Report on Alternative Medicine, Lancet, 1, 1223

Anon, 1986c, Alternative Medicine, Lancet, 2, 116-117

Anon, 1986d, Magic or Medicine?, Which?, October, 443-447

Anon, 1986e, Alternative Therapy, London: British Medical Association

Anon, 1986f, No scientific basis for homoeopathy (editorial), Pharm.J., 236, 745-746

Anon, 1987a, The AHPA Herb Standard Program, Herbalgram, No 12, 2

Anon, 1987b, New university unit for complementary medicine, Pharm.J., 239, 210

Anon, 1988a, Want to learn?, Chemist & Druggist, 26 November, 937

Anon, 1988b, Pyrrolizidine Alkaloids: Environmental Health Criteria 80, Geneva: World Health Organisation

Anon, 1989a, Squill, Lawrence Review of Natural Products

Anon, 1989b, Hypericin - a plant extract with anti-HIV activity, Scrip, 1415, 29

Anon, 1989c, Quality of Herbal Remedies. *The Rules Governing Medicinal Products in the European Community*, vol. III, 31-37

Anon, 1989d, Medicines Act Leaflet (MAL) 2. Guidelines on Safety and Efficacy Requirements for Herbal Medicinal Products. *Guidance Notes on Applications for Product Licences*, London: Medicines Control Agency

Anon, 1990a, Gamolenic acid in atopic eczema: Epogam, Drug Ther.Bull., 28, 69-70

Anon, 1990b, Society appeals for controls on unlicensed natural remedies, Pharm.J., 245, 808

Anon, 1990c, European Scientific Cooperative for Phytotherapy (ESCOP). *Proposals for European Monographs*, vol.1 1990, vol.2 1992, vol.3 1992, Meppel, Netherlands: ESCOP

Anon, 1992a, Chaparral-induced toxic hepatitis - California and Texas, Morbidity Mortality Weekly Report, 41, 812-4

Anon, 1992b, Manufacture of Herbal Medicinal Products. *The Rules Governing Medicinal Products in the European Community*, vol. IV, 127-129

Anon, 1993a, Toxic tea, Pharm.J., 250, 366

Anon, 1993b, The Osteopaths Bill, Br.Med.J., 306, 1556-1557

Anon, 1993c, Complementary Medicine: New Approaches to Good Practices, Oxford: British Medical Association

Anon, 1993d, CPMP Working Party on Quality of Medicinal Products. *Note for Guidance: Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products*, III/9261/90-EN Final

Anon, 1994a, Statutory Instrument (SI) 1994: 3144, The Medicines for Human Use (Marketing Authorisations Etc.) Regulations, London: HMSO

Anon, 1994b, The safety-in-use of comfrey and comfrey products. Research survey. 24 June 1994. Heathfield, East Sussex: Society for the Promotion of Nutritional Therapy

Anon, 1995a, Hypericin improves blood safety?, Scrip, 2005, 27

Anon, 1995b, Hypericin HIV trial in Thailand, Scrip, 2019, 29-30

Anon, 1995c, ABPI Data Sheet Compendium 1995-1996, London: Datapharm Publications Limited

Anon, 1995d, Medicines Act Leaflet (MAL) 8. A Guide to What a Medicinal Product Is, London: Medicines Control Agency

Anon, 1996a, Martindale, The Extra Pharmacopoeia 31st edition (ed. JEF Reynolds), London: Royal Pharmaceutical Society

Anon, 1996b, Paclitaxel now licensed for first-line use in treatment of ovarian cancer, Pharm.J., 257, 631

Anon, 1996c, Phytopharm's eczema herbs, Pharm.J., 257, 630

Anon, 1996d, Staying Healthy, Chemists & Druggists (supplement), March 9, 14

Anon, 1996e, Melatonin Potentially Useful but Safety, Efficacy Remain Uncertain, JAMA, 276, 1011-1014

Anon, 1996f, Alternative Medicine: The Renewed Interest in Health Care, Pharmaceutical News, 3, 19-22

Anon, 1996g, Evidence for benefit of St. John's Wort in depressive disorders (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 770

Anon, 1996h, "Promising future" for mistletoe lectins as immunomodulator agents (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 770

Anon, 1996i, Novel anticancer compounds from nature (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 771

Anon, 1996j, Research suggests possible mechanisms for sedative action of valerian (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 771

Anon, 1996k, Promising leads identified by screening programmes (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 771

Anon, 1996l, Hope for hawthorn in heart failure (Second International Congress on Phytomedicine, Sept. 11-14, 1996, Munich, Germany), Pharm.J., 257, 771

Anon, 1996m, Need for plant drug research, Pharm.J., 257, 639

Anon, 1996n, Plant promises and potential perils, Pharm.J., 257, 639

Anon, 1996o, Value of Mediterranean plants, Pharm.J., 257, 639

Anon, 1996p, Extension of the Yellow Card scheme to unlicensed herbal remedies, Current Problems in Pharmacovigilance, 22, 10

Anon, 1996q, PAGB's ginkgo complaint upheld, Pharm.J., 257, 881

Anon, 1996r, Policy Report - Dietary Supplements, London: Consumers Association

Anon, 1996s, BfArM's ruling on laxatives based on insufficient evidence, says BAH, OTC bulletin, No.68, 9

Anon, 1996t, British Herbal Pharmacopoeia, London: British Herbal Medicine Association

Anon, 1996u, The Merck Index 12th edition (ed. S.Budavari), New Jersey: Merck & Co., Inc.

Anon, 1996v, Casarett & Doull's Toxicology: The Basic Science of Poisons 5th edition (ed. CD Klaassen)

Anon, 1997a, European Pharmacopoeia, London: The Pharmaceutical Press

Anon, 1997b, Latest POM Order changes - no new P ingredients, Pharm.J., 258, 87

Anyanwu CH & Okonkwo PO, 1981, Oesophageal strictures induced by herbal preparations, Transactions of the Royal Society of Tropical Medicine and Hygiene 75, 864-868

Applebe GE & Wingfield J, 1993, Dale and Applebe's Pharmacy Law and Ethics 5th edition, London: The Pharmaceutical Press

Armanini D, Karbowiak I & Funder JW, 1983, Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors, Clin.Endocrinol., 19, 609-612

Armanini D, Strasser T & Weber PC, 1985, Binding of agonists and antagonists to mineralocorticoid receptors in human peripheral mononuclear leucocytes, J.Hypertens., 3 (Suppl 3): S157-159

Ashwood-Smith MJ, Ceska O & Chaudhary SK, 1985, Mechanisms of photosensitivity reactions to diseased celery, Br.Med.J., 290, 1249

Aslam M, Davis SS & Healy MA, 1979, Heavy metals in some Asian medicines and cosmetics, Public Health 93, 274-284

Aslam M, Healy MA, Davis SS & Ali AR, 1980, Surma and blood lead in children, Lancet 1, 658-659

Aulfat RA, Smales ORC & Aslam M, 1978, Surma and lead poisoning, Br.Med.J., 2, 915-916

Austad J & Kavli G, 1983, Phototoxic dermatitis caused by celery infected by *Sclerotinia sclerotiorum*, Contact Dermatitis, 9, 448-51

Auty RM, 1993, Drug Development (Chapter 3) *in* A Textbook of Pharmaceutical Medicine: Current Practice (eds. RD Mann, MD Rawlins, RM Auty), Parthenon Publishing Group Limited: Carnforth, *pp* 19-39

Awang DVC, 1993, Feverfew fever - a headache for the consumer, Herbalgram, No. 29, 34-36, 66

Ayres DC & Loike JD, 1990, Lignans - chemical, biological and clinical properties *in* Chemistry and Pharmacology of Natural Products series (series eds. JD Phillipson, DC Ayres & H Baxter), Cambridge: Cambridge University Press

Balderer G & Borbely AA, 1985, Effect of valerian on human sleep, Psychopharmacology, 87, 406-409

Baldwin CA, Anderson LA & Phillipson JD, 1986, What pharmacists should know about ginseng, The Pharm.J., 237, 583-6

Baldwin CA, Anderson LA & Phillipson JD, 1987a, What pharmacists should know about feverfew, Pharm.J., 239, 237-8

Baldwin CA, Anderson LA & Phillipson JD, 1987b, Storm in a herbal teacup?, The Pharm.J., 239, R10

Baldwin CA, Anderson LA, Phillipson JD & Spencer MG, 1987c, Drug information - herbal concern, Pharm.J., 239, R13

Bamford JTM, Gibson RW & Renier CM, 1985, Atopic eczema unresponsive to evening primrose oil (linolenic and gamma-linolenic acids), J.Am.Acad.Dermatol., 13, 959-965

Bannister B, Ginsburg R & Shneerson J, 1977, Cardiac arrest due to liquorice-induced hypokalaemia, Br.Med.J., 2, 738-739

Baranov AI, 1982, Medicinal uses of ginseng and related plants in the Soviet Union: recent trends in the Soviet literature, J.Ethnopharmacol., 6, 339-53

Barber AJ, 1988, Evening primrose oil: a panacea?, Pharm.J., 240, 723-725

Barker BE, Farnes P & Fanger H, 1965, Mitogenic activity in *Phytolacca americana* (pokeweed), Lancet, 1, 170

Barker BE, Farnes P & LaMarche PH, 1966, Peripheral blood plasmacytosis following systemic exposure to *Phytolacca americana* (pokeweed), Paediatrics, 38, 490-3

Barker BE, Farnes P & LaMarche PH, 1967, Haematological efffects of pokeweed, Lancet, 1, 437

Barnes J, 1997, Complementary health care symposium attracts worldwide audience, Pharm.J., 258, 76-77

Barsby RWJ, Salan U, Knight DW & Hoult JRS, 1993, Feverfew and Vascular Smooth Muscle: Extracts from Fresh and Dried Plants Show Opposing Pharmacological Profiles, Dependent Upon Sesquiterpene Lactone Content, Planta Medica, 59, 20-25

Benoit PS, Fong HHS, Svoboda GH & Farnsworth NR, 1976, Biological and phytochemical evaluation of plants. XIV. Antiinflammatory evaluation of 163 species of plants. Lloydia, 39, 160-171

Berghofer R & Holzl J, 1987, Biflavonoids in *Hypericum perforatum*; Part 1. Isolation of 13,II8-biapigenin, Planta Med., 53, 216-217

Berkley SF, Hightower AW, Beier RC, Fleming DW, Brokopp CD, Wayne G & Broome CV, 1986, Dermatitis in grocery workers associated with high natural concentrations of furanocoumarins in celery, Annals of Internal Medicine, 105, 351-5

Berry M, 1994, Feverfew, Pharm.J., 253, 806-808

Berry M, 1995, The chamomiles, Pharm.J., 254, 191-193

Berth-Jones J & Graham-Brown RAC, 1993, Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis, Lancet, 341, 1557-1560

Bingham R, Bellew BA & Bellew JG, 1975, Yucca plant saponin in the management of arthritis, J.Appl.Nutr., 27, 45-51

Bingham R, Harris DH & Laga T, 1978, Yucca plant saponin in the treatment of hypertension and hypercholesterolemia, J.Appl.Nutr., 30, 127-136

Bisler H, Pfeifer R, Kluken N & Pauschinger P, 1986, Wirkung von Rosskastaniensamenextrakt auf die transkapillare Filtration bei chronischer venoser Insuffizienz, Dtsch.Med.Wochenschr, 111, 1321-1329

Bisset NG (ed.), 1994, Herbal drugs and phytipharmaceuticals (Wichtl M (ed.) German edition), Stuttgart: Medpharm

Bloksma N, Schmiermann P, de Reuver M, van Dijk H & Willers J, 1982, Stimulation of humoral and cellular immunity by *Viscum* preparations, Planta Medica, 46, 221-7

Bock KW & Schirmer G, 1987, Species differences of glucuronidation and sulfation in relation to hepatocarcinogenesis, Archives of Toxicology, 10(Suppl), 125-35

Boisset M & Fitzcharles MA, 1994, Alternative medicine use by rheumatology patients in a universal health care setting, J.Rheumatol., 21, 148-152

Bosse J-P, Papillon J, Frenette G, Dansereau J, Cadotte M & LeLorier J, 1979, Clinical study of a new antikeloid agent, Ann.Plast.Surg., 3, 13-21

Braquet P, 1987, The ginkgolides: potent platelet-activating factor antagonists isolated from *Ginkgo biloba* L.: Chemistry, pharmacology and clinical applications, Drugs of the Future, 12, 643-699

Braquet P (ed.), 1988, Ginkgolides - chemistry, biology, pharmacology and clinical perspectives, vol. 1, Barcelona: JR Prous

Braquet P (ed.), 1989, Ginkgolides - chemistry, biology, pharmacology and clinical perspectives, vol. 2, Barcelona: JR Prous

Brevoort P, 1996, Botanical (Herbal) Medicine in the United States, Pharmaceutical News, 3, 26-28

Britt RAJ, 1995, The New EC Systems In The UK, The Regulatory Affairs Journal, May, 380-384

Brooks PM & Lowenthal RM, 1977, Chinese herbal arthritis cure and agranulocytosis, Med.J.Aust., 2, 860-861

Bruckner C, 1989, In mitteleuropa gentzte heilpflanzen mit milchsekretionsfordernder wirkung (galactagoga), Gleditschia, 17, 189-201

Bruno M, Piozzi F, Savona G, De La Torre MC & Rodriguez B, 1989, Neo-clerodane diterpenoids from *Teucrium canadense*, Phytochemistry, 28, 3539-3541

Bryson PD, Watanabe AS, Rumack BH & Murphy RC , 1978, Burdock root tea poisoning. Case report involving a commercial preparation, JAMA, 239, 2157-8

Buck AC, 1996, Phytotherapy for the prostate (Review), Br.J.Urology, 78, 325-336

But PPH, 1993, Need for correct identifcation of herbs in herbal poisoning, Lancet 341, 637

Buurma H, de Kaste D & Vulto AG, 1983, Drugs Used in Non-Orthodox Medicine *in* Side Effects of Drugs Annual 7 (ed. MNG Dukes), Amsterdam: Excerpta Medica, pp462-473

Buurma H & Vulto AG, 1984, Drugs Used in Non-Orthodox Medicine *in* Side Effects of Drugs Annual 8 (ed. MNG Dukes), Amsterdam: Elsevier Science

Capasso F, 1986, The effect of an aqueous extract of *Tanacetum parthenium* L. on arachidonic acid metabolism by rat peritoneal leucocytes, J.Pharm.Pharmacol., 38, 71-72

Carilla E, Briley M, Fauran F, Sultan Ch. & Duvilliers C, 1984, Binding of permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate, J.Steroid Biochem., 20, 521-523

Carreras JO, 1987, Nuestra experiencia con extracto hexanico de *Serenoa repens* en el tratamiento de la hipertrofia benigna de prostata, Arch.Esp. de Urol., 40, 310-313

Cebo B, Krupinska J, Sobanski H, Mazur J & Czarnecki R, 1976, Pharmacological properties of saponin fractions from Polish crude drugs: Saponaria officinalis, Primula officinalis, and Aesculus hippocastanum, Herba Pol., 22, 154-162

Chamberlain TJ, 1970, Licorice poisoning, pseudoaldosteronism, heart failure, JAMA, 213, 1343

Champault G, Patel JC & Bonnard AM, 1984, A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia, Br.J.Clin.Pharmac., 18, 461-462

Chandler RF, Anderson LA & Phillipson JD, 1984a, Laetrile in perspective, Canadian Pharm.J., 117, 517-520

Chandler RF, Anderson LA, and Phillipson JD, 1984b, Controversial laetrile, Pharm.J., 232, 330-332

Chaplin S, 1994, Chinese herbal remedies for refractory eczema, Prescriber 5, 64-66

Chaudhary SK, Oldriska C, Warrington PJ & Ashwood-Smith MJ, 1985, Increased furocoumarin content of celery during storage, J.Agric.Food Chem., 33, 1153-1157

Christen Y, Droy-Lefaix MT & Macias-Nunez (eds), 1995, Advances in *Ginkgo biloba* extract research, volume 5: Effects of *Ginkgo biloba* extract (Egb761) on neuronal plasticity (Proceedings of the International Symposium, Salamanca, Spain, 30.9.95), Amsterdam: Elsevier

Chung KF, 1987, Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man, Lancet, 1, 248-251

Cibelli G, DeMari M, Pozio G & Lamberti P, 1984, Hypokalemic myopathy associated with liquorice ingestion, Ital.J.Neurol.Sci., 5, 463-466

Clark F & Reed R, 1992, Chaparral-induced toxic hepatitis - California and Texas, Morb.Mortal. Weekly Report, 41, 812-814

Collier HOT, Butt NM, McDonald-Gibson WJ & Saeed SA, 1980, Extract of feverfew inhibits prostaglandin biosynthesis, Lancet, 2, 922-923

Collin MA & Charles HP, 1987, Antimicrobial activity of carnosol and ursolic acid: two anti-oxidant constituents of *Rosmarinus officinalis* L., Food Microbiol., 4, 311-315

Conn JW, Rovner DR & Cohen EL, 1968, Licorice-induced pseudoaldosteronism. Hypertension, hypokalaemia, aldosteronopenia and suppressed plasma renin activity, JAMA, 205, 492-496

Conway GA & Slocumb JC, 1979, Plants used as abortifacients and emmenagogues by Spanish New Mexicans, J.Ethnopharmacol., 1, 241-261

Cook T, 1989, Homoeopathic Medicine Today, USA: Keats Publishing Inc.

Cooper MR & Johnson AW, 1984, Poisonous plants in Britain and their effects on Animals and Man. Ministry of Agriculture, Fisheries and Foods Reference Book 101, London: HMSO, pp305

Cootes P, 1982, Clinical curio: liver disease and parsley, Br.Med.J., 285, 1719

Corres LF, 1984, Contact dermatitis from *Frullania*, Compositae and other plants, Contact Dermatitis, 11, 74-79

Corrocher R, Corradi T, Miatto O, Bonfanti F & De Sandre G, 1983, Pseudoprimary hyperaldosteronism due to liquorice intoxication, Eur.Rev.Med.Pharmacol.Sci., 5, 467-470

Cosyns J-P, Jadoul M, Squifflet J-P, De Plaen J-F, Ferluga D & Van Ypersele de Strihou C, 1994, Chinese herbs nephropathy: a clue to Balkan endemic nephropathy, Kidney International 45, 1680-88

Cosyns JP, Jadoul M, Squifflet J-P, Van Cangh P-J & Van Ypersele de Strihou C, 1994, Urothelial malignancy in nephropathy due to Chinese herbs, Lancet, 344, 188

Court WE, 1985, Squill - energetic diuretic, Pharm.J., 235, 194-197

Cranz H, 1994, Medicinal plants and phytomedicines within the European Community, Herbalgram, 30, 50-53

Culvenor CCJ, 1985, Pyrrolizidine alkaloids: some aspects of the Australian involvement, TIPS, 6, 18-22

Culvenor CCJ, Edgar JA, Smith LW & Hirono L, 1976, The occurrence of senkirkine in *Tussilago farfara*, Aust.J.Chem., 29, 229-230

Culvenor CCJ, Edgar JA, Smith LW, Kumana CR & Lin HJ, 1986, *Heliotropium lasiocarpum* Fisch & Mey Identified as cause of Veno-Occlusive Disease due to a Herbal Tea, Lancet 1, 978

D'Arcy PF, 1991, Adverse reactions and interactions with herbal medicines. Part 1 - Adverse Reactions, Adverse Drug React.Toxicol.Rev., 10, 189-208

D'Arcy PF, 1993, Adverse reactions and interactions with herbal medicines. Part 2 - Drug Interactions, Adverse Drug React Toxicol Rev, 12, 147-162

Danesi MA & Adetunji JB, 1994, Use of alternative medicine by patients with epilepsy: a survey of 265 epileptic patients in a developing country, Epilepsia, 35, 344-351

Datta DV, Khuroo MS, Mattocks AR, Aikat BK & Chhuttani PN, 1978a, Herbal medicines and veno-occlusive disease in India, Postgrad.Med.J., 54, 511-515

Datta DV, Khuroo MS, Mattocks AR, Aikat BK & Chhuttani PN, 1978b, Veno-occlusive disease of the liver due to *Heliotropium* plant used as medicinal herb (report of six cases with review of literature), J.Assoc.Phys.India, 26, 383-393

Deboyser P, 1991, Traditional herbal medicines around the globe: Modern Perspectives. The assessment of herbal remedies in the EC, Swiss Pharma, 13, 86-89

Dechamp C, Michel J, Deviller P & Perrin LF, 1984, Choc anaphylactique au celeri et sensibilisation a l'ambroisie. Allergie croisee ou allergie concomitante?, Presse Med., 13, 871-874

De Pascale V, Bamonte F, Lavezzari E, Craveri F, Frigo GM & Crema A, 1974, Effect of an escin-cyclonamine mixture on capillary permeability, Boll.Chim.Farm., 113, 600-614

De Smet PAGM, 1989, Dutch patient information on the safe use of herbal remedies, International Pharmacy Journal, 3, 98-101

De Smet PAGM, 1992, Drugs used in non-orthodox medicine *in* Meyler's Side Effects of Drugs Annual 12th edition (ed. MNG Dukes), Amsterdam: Elsevier, pp1209-1232

DeSmet PAGM, 1995, Health risks of herbal remedies, Drug Safety, 13, 81-93

De Smet PAGM, Keller K, Hansel R & Chandler RF (eds.), 1992, Adverse effects of herbal drugs vol. 1, Berlin: Springer Verlag

De Smet PAGM, Keller K, Hansel R & Chandler RF (eds.), 1993, Adverse effects of herbal drugs vol. 2, Berlin: Springer Verlag

Dewick PM, 1982, Isoflavonoids *in* The Flavonoids: Advances in Research (eds. JB Harbourne & TJ Mabry), London: Chapman & Hall, pp535-640

Dolan G, Jones AP, Blumsohn A, Reilly JT & Brown MJ, 1991, Lead poisoning due to Asian ethnic treatment for impotence, J.R.Soc.Med, 84, 630-631

Donnelly WJ, Spykerboer JE & Thong YH, 1985, Are patients who use alternative medicine dissatisfied with orthodox medicine?, Med.J.Aust., 142, 539-541

Duke JA, 1985, Handbook of medicinal herbs, Boca Raton: CRC

Dukes MNG, 1977, Remedies used in non-orthodox medicine *in* Side Effects of Drugs Annual (ed. MNG Dukes), Amsterdam: Excerpta Medica, pp371-378

Dukes MNG, 1980, Drugs used in non-orthodox medicine *in* Meyler's Side Effects of Drugs (ed. MNG Dukes) 9th ed., Amsterdam: Excerpta Medica, pp786-795

Dukes MNG, 1994, Drugs used in non-orthodox medicine *in* Side Effects of Drugs Annual 17 (1993), (eds. JK Aronson & CJ Van Boxtel), Amsterdam: Elsevier Science, pp545-550

Edwards C & Stillman P, 1995, Minor Illness or Major Disease 2nd edition, London: The Pharmaceutical Press, pp115

Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR & Delbanco TL, 1993, Unconventional medicine in the United States - Prevelance, Costs and Patterns of Use, NEJM, 328, 246-252

Elliott-Binns CP, 1986, An analysis of lay medicine: fifteen years later, J.R.Coll.Gen.Pract., 36, 542-544

Ernst E & Barnes J, 1996, Establishing impartiality, Pharm.J., 257, 702

Evans WC, 1996, Trease & Evans' Pharmacognosy 14th edition, London: WB Saunders Co. Ltd.

Farnsworth NR & Cordell GA, 1976, A review of some biologically active compounds isolated from plants as reported in the 1974-1975 literature, Lloydia, 39, 420-455

Farnsworth NR, Kinghorn AD, Soejarto DD & Waller DP, 1985, Siberian ginseng (*Eleutherococcus senticosus*): Curent status as an adaptogen *in* Economics and Medicinal Plant Research, vol. 1 (eds. Wagner H et al), London: Academic Press, 155-209

Finberg M, 1996, Opportunities for the open minded, Pharm.J., 257, 394

Fisher P & Ward A, 1994, Complementary medicine in Europe, Br.Med.J., 309, 107-110

Forsbeck M & Ros A-M, 1979, Anaphylactoid reaction to celery, Contact Dermatitis, 5, 191

Forslund T, Fyhrquist F, Froseth B & Tikkanen I, 1989, Effects of licorice on plasma atrial natriuretic peptide in healthy volunteers, J.Intern.Med., 225, 95-99

Forster PJG, Calverley M, Hubball S & McConkey B, 1979, Chuei-Fong-Tou-Geu-Wan in rheumatoid arthritis, Br.Med.J., 2, 308

Fox DW, Hart MC, Bergeson PS, Jarret PB, Stillman AE & Huxtable RJ, 1978, Pyrrolizidine (*Senecio*) intoxication mimicking Reye syndrome, J.Pediatr., 93, 980-982

Franz H, Ziska P & Kindt A, 1981, Isolation and properties of three lectins from mistletoe (*Viscum album* L.), Biochemical Journal, 195, 481-484

Frohne D & Pfander HJ, 1984, A colour atlas of poisonous plants, London: Wolfe

Fujita H, Sakurai T, Yoshida M & Toyoshima S, 1980, Anti-inflammatory effect of glycyrrhizinic acid. Effects of glycyrrhizinic acid against carageenin-induced edema, UV-erythema and skin reaction sensitised with DCNB, Pharmacometrics, 19, 481-484

Fulder S, 1984, The Handbook of Complementary Medicine, London: Coronet

Fulder S & Munro RE, 1985, Complementary medicine in the United Kingdom: Patients, practitioners and consultations, Lancet, 2, 542-545

Furmanowa M, Guzewska J & Beldowska B, 1983, Mutagenic effects of aqueous extracts of *Symphytum officinale*L. and of its alkaloidal fractions, J.Appl.Toxicol., 3, 127-130

Furnham A & Forey J, 1994, The attitudes, behaviours and beliefs of patients of conventional vs. complementary (alternative) medicine, J.Clin.Psychol., 50, 458-469

Geiger H & Quinn C , 1982, Biflavonoids *in* The Flavonoids: Advances in Research (eds. JB Harbourne & TJ Mabry), London: Chapman & Hall

Goggelmann W & Schimmer O, 1983, Mutagenicity testing of b-asarone and commercial calamus drugs with *Salmonella typhimurium*, Mutation Research, 121, 191-194

Goldman JA, 1991, Chinese herbal medicine: camouflaged precription antiinflammatory drugs, corticosteroids and lead, Arthritis and Rheumatism, 34, 1207

Gordon DW, Rosenthal G, Hart J, Sirota R & Baker AL, 1995, Chaparral ingestion - the broadening spectrum of liver injury caused by herbal medicines, JAMA, 273, 489-490

Graham-Brown R, 1992, Toxicity of Chinese herbal remedies, Lancet, 340, 673

Grasso A & Corvaglia E, 1976, Two cases of suspected toxic tubulonephrosis due to escine, Gazz Med Ital, 135, 581-584

Grontved A, Brask T, Kambskard J & Hentzerr E, 1988, Ginger root against seasickness. A controlled trial on the open sea, Acta Otolaryngol, 105, 45-49

Gross MA, Jones WI, Cook EL & Boone CC, 1967, Carcinogenicity of oil of calamus, Proc.Amer.Ass. Cancer Res, 8, 24

Guenther E, 1948-1952, The Essential Oils, 6 volumes, New York: Van Nostrand

Gunby P, 1979, Plant known for centuries still causes problems today, JAMA, 241, 2246-2247

Gunn JWC, 1921, The action of the "Emmenagogue Oils" on the human uterus, J Pharmacology and Experimental Therapeutics, 16, 485-489

Gupta PS. Gupta GD & Sharma ML, 1963, Veno-occlusive disease of the liver, Br.Med.J., 1, 1184-1186

Guslandi M, 1985, Ulcer-healing drugs and endogenous prostaglandins, Int.J.Clin.Pharmacol.Ther.Toxicol., 23, 398-402

Hall AH, Spoerke DG & Rumack BH, 1986, Assessing mistletoe toxicity, Ann.Emerg.Med., 15, 1320-1323

Hamon NW & Blackburn JL, 1985, Herbal products - a factual appraisal for the health care professional, Winnipeg: Cantext

Hardin JW & Arena JM (eds.), 1974, Human poisoning from native and cultivated plants (2nd edition), North Carolina: Duke University, 150-153

Harper J, 1994, Traditional Chinese medicine for eczema: Seemingly effective, but caution must prevail, Br.Med.J., 308, 489-499

Harvey J & Colin-Jones D-G, 1981, Mistletoe hepatitis, Br.Med.J., 282, 186-187

Haslem E, 1989, Plant polyphenols: vegetable tannins revisited *in* Chemistry and Pharmacology of Natural Products series (series eds. JD Phillipson, DC Ayres & H Baxter), Cambridge: Cambridge University Press

Hausen BM, 1979, The sensitising capacity of Compositae plants III: Test results and cross-reactions in Compositae-sensitive patients, Dermatologica, 159, 1-11

Hausen BM & Osmundsen PE, 1983, Contact allergy to parthenolide in *Tanacetum parthenium* (L.) Schulz-Bip. (Feverfew, Asteraceae) and cross-reactions to related sesquiterpene lactone containing Compositae species, Acta.Derm.Venereol. (Stockh.), 63, 308-314

Heath D, Shaba J, Williams A, Smith P & Kombe A, 1975, A pulmonary hypertension-producing plant from Tanzania, Thorax, 30, 399-404

Heidermann HT & Kreuzfelder E, 1983, Hypokalemic rhabdomyolysis with myoglobinuria due to licorice ingestion and diuretic treatment, Klin.Wochenschr, 61, 303-305

Helman CG, 1994, Caring and curing: the sectors of healthcare (Chapter 4) *in* Culture, Health and Illness: An Introduction for Health Professionals (3rd edition), Oxford: Butterworth-Heinemann

Hendriks H, Bos R, Woerdenbag HJ & Koster AS, 1985, Central nervous depressant activity of valerenic acid in the mouse, Planta Med., 51, 28-31

Heptinstall S, Williamson L, White A & Mitchell JRA, 1985, Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes, Lancet, 1, 1071-1073

Himmel W, Schulte M & Kochen MM, 1993, Complementary medicine: are patients' expectations being met by their general practitioners?, Br.J.Gen.Pract., 43, 232-235

Hindmarsh SZ, 1984, The psychopharmacological effects of *Ginkgo biloba* extract in normal healthy volunteers, Int.J.Clin.Pharmacol.Res., 4, 89-93

Hirono I, Mori H & Haga M, 1978, Carcinogenic activity of *Symphytum officinale*, J.Natl. Cancer Inst., 61, 865-869

Hirono I, Mori H, Haga M, Fujii M, Yamada K, Hirata Y, Takanashi H, Uchida E, Kosaka S, Keno J, Matsushima T, Umezawa K & Shirai A, 1979, Edible plants containing carcinogenic alkaloids in Japan *in* Miller EC (ed.), Naturally occurring carcinogens - mutagens and modulators of carcinogenesis, Tokyo, Baltimore: Japan Sci.Soc.Press, Univ. Park Press, pp79-87

Hobbs C, 1988, Sarsaparilla: A literature review, Herbalgram, No.17, 1, 10-15

Hobbs C & Foster S, 1990, Hawthorn: A literature review, Herbalgram, No. 22, 19-33

Hof S & Ammon HPT, 1989, Negative inotropic action of rosemary oil, 1,8-cineole, and bornyl acetate, Planta Med., 55, 106-107

Hoffman D, 1996, The Complete Illustrated Holistic Herbal, Shaftsbury, Dorset: Element Books Ltd., pp256

Hoffman FA & Leaders FE, 1996, Botanical (herbal) medicine in health care: A review from a regulatory perspective, Pharmaceutical News, 3, 23-25

Holzbecher MD, Moss MA & Ellenberger HA, 1984, The cyanide content of laetrile preparations, apricot, peach and apple seeds, Clin.Toxicol., 22, 341-347

Homburger F & Boger E, 1968, The carcinogenicity of essential oils, flavors, and spices: A review, Cancer Res., 28, 2372-2374

Hoppe HA, 1981, Taschenbuch der drogenkunde, Berlin: de Gruyter

Horrobin DF, 1990, Gammalinolenic acid: an intermediate in essential fatty acid metabolism with potential as an ethical pharmaceutical and as a food, Rev.Contemp.Pharmacother., 1, 1-45

Hostettmann K & Marston A, 1995, Saponins *in* Chemistry and Pharmacology of Natural Products series (series eds. JD Phillipson, DC Ayres & H Baxter), Cambridge: Cambridge University Press

Hostettmann K, Marston A & Wolfender JL, 1995, Strategy in the search for new biologically active plant constituents *in* Phytochemistry of Plants Used in Traditional Medicine (eds. K.Hostettman, A.Marston, M.Maillard & M.Hamburger), Oxford: Oxford University Press

Houghton PJ, 1994a, Valerian, Pharm.J., 253, 95-96

Houghton PJ, 1994b, Ginkgo, Pharm.J., 253, 122-123

Houghton PJ, 1994c, Echinacea, Pharm.J., 253, 342-343

Houghton PJ, 1994d, Agnus castus, Pharm.J., 253, 720-721

Houghton PJ, 1995, Guarana, Pharm.J., 254, 435-436

Howard JR, 1993, Pharmacy and pharmaceutical development (Chapter 7) *in* A Textbook of Pharmaceutical Medicine: Current Practice (eds. RD Mann, MD Rawlins & RM Auty), Carnforth: Parthenon Publishing Group Ltd.

Hudson JB, Graham EA & Towers GHN, 1994, Antiviral assays on phytochemicals: The influence of reaction parameters, Planta Med., 60, 329-332

Huxtable RJ, 1980, Herbal teas and toxins: novel aspects of pyrrolizidine poisoning in the United States, Perspect.Biol.Med., 24, 1-14

Huxtable RJ, 1990, The harmful potential of herbal and other plant products, Drug Safety, 5, 126-136

Huxtable RJ, 1992, The myth of beneficient nature: The risks of herbal preparations, Annals Int.Med., 117, 165-166

Huxtable RJ, Luthy J & Zweifel U, 1986, Toxicity of comfrey-pepsin preparations, NEJM, 315, 1095

Hyde FF, 1978, The origin and practice of herbal medicine, Mims Magazine, 2, 127-136

Inglis B, 1992, Unorthodox medicine after the establishment of the National Health Service *in* Alternative Medicine in Britain (ed. M Saks), Oxford: Clarendon Press

Ioannides C, Delaforge M & Parke DV, 1981, Safrole: its metabolism, carcinogenicity and interactions with cytochrome P-450, Food Cosmet.Toxicol., 19, 657-666

Ioannides C, Delaforge M & Parke DV, 1985, Interactions of safrole and isosafrole and their metabolites with cytochrome P-450, Chem.Biol.Interactions, 53, 303-311

Israelsen LD, 1996, Botanicals: A current regulatory perspective for the United States. Presented at the INDENA workshop on "From act to actions when dealing with botanicals", Milan, September 9, 1996

Iwasaki K, Lum PY, Ioannides C & Parke DV, 1986, Induction of cytochrome P-488 activity as exemplified by the *o*-deethylation of ethoxyresorufin. Effects of dose, sex, tissue and animal species, Biochem.Pharmacol., 35, 3879-3884

Jacker H-J, Voigt G & Hiller K, 1982, Zum antiexsudativen Verhalten einiger Triterpensaponine, Pharmazie, 37, 380-382

Jadhav SJ, Salunkhe DK, Kadam SS, Chavan JK & Ingle UM, 1982, Pyrrolizidine Alkaloids: A Review, J.Food Sci.Tech., 19, 87-93

Jahodar L, Jilek P, Patkova M & Dvorakova V, 1985, Antimicrobial action of arbutin and the extract from the leaves of *Arctostaphylos uva-ursi* in-vitro, Ceskoslov Farm, 34, 174-178

Jakovlev V, Isaac O, Thiemer K & Kunde R, 1979, Pharmacological investigations with compounds of chamomile II. New investigations on the antiphlogistic effects of (-)-α-bisabolol and bisabolol oxides, Planta Med., 35, 125-140

Jalsenjak V, Peljnjak S & Kustrak D, 1987, Microcapsules of sage oil: Essential oils content and antimicrobial activity, Pharmazie, 42, 419-420

Jamil A, Luqman W & Emara M, 1986, Hyperglycaemia related to licorice-induced hypokalaemia, J.Kwt.Med.Assoc., 20, 69-71

Johnson ES, Kadam NP, Hylands DM & Hylands PJ, 1985, Efficacy of feverfew as prophylactic treatment of migraine, Br.Med.J., 291, 569-573

Jolad SD, Bates RB, Cole JR, Hofmann JJ, Siahaan TJ & Timmermann BN, 1986, Cardenolides and a lignan from *Asclepias subulata*, Phytochemistry, 25, 2581-2590

Kartnig T, 1986, *Vitex agnus-castus* - Monchspfeffer oder Keuschlamm. Ein arneipflanze mit indirekt-luteotroper wirkung., Z.Phytotherapie, 7, 119-122

Kartnig T, 1988, Clinical applications of *Centella asciatica* (L.)Urb. *in* Herbs, Spices and Medicinal Plants: Recent Advances in Botany, Horticulture and Pharmacology Vol. 3 (eds. LE Craker & JE Simon), Arizona: Oryx Press

Katz M & Saibil F, 1990, Herbal hepatitis: subacute hepatic necrosis secondary to chaparral leaf tea, J.Clin.Gastroenterol., 12, 203-206

Kayne S, 1996, No need to squabble, Pharm.J., 257, 658

Keller K, 1993, Therapeutic use of herbal drugs and their potential toxicity. Problems and results of the revision of herbal remedies in the EEC. (Proceedings of a lecture held in Rome), European Phytotelegram, 5th issue, 15-22

Keller K, 1994, Phytotherapy at a European level, European Phytotelegram, 6th issue, 40-45

Keller K & Stahl E, 1983, Zusammensetzung des atherischen Oles von β-asaronfreiem Kalmus, Planta Med., 47, 71-74

Kestin M, Miller L, Littlejohn G & Wahlqvist M, 1985, The use of unproven remedies for rheumatoid arthritis in Australia, Med.J.Aust., 143, 516-518

Kew J, Morris C, Aihie A, Fysh R, Jones S & Brooks D, 1993, Arsenic and mercury intoxication due to Indian ethnic remedies, Br.Med.J., 306, 506-507

Kimbel KH, 1979, Br.Med.J., 2, 669 (letter)

Kiso Y, Tohkin M, Hikino H, Hattori M, Sakamoto T & Namba T, 1984, Mechanism of antihepatotoxic activity of glycyrrhizin, I: Effect on free radical generation and lipid peroxidation, Planta Med., 50, 298-302

Kiuchi F, Shibuya M & Sankawa U, 1982, Inhibitors of prostaglandin biosynthesis from ginger, Chem.Pharm.Bull., 30, 754-757

Knight DW, 1995, Feverfew: Chemistry and biological activity, Nat.Prod.Rep., 12, 271-276

Kshirsagar NA, 1993, Misleading herbal Ayurvedic brand name, Lancet, 341, 1595-1596

Kumana CR, Ng M, Lin HJ, Ko W, Wu P-C & Todd D, 1983, Hepatic veno-occlusive disease due to toxic alkaloid in herbal tea, Lancet, 2, 1360-1361

Kumana CR, Ng M, Lin HJ, Ko W, Wu P-C & Todd D, 1985, Herbal tea induced hepatic veno-occlusive disease: quantification of toxic alklaoid exposure in adults, Gut, 26, 101-104

Kumar A, Sharma VD, Singh AK & Singh K, 1988, Antibacterial properties of some *Eucalyptus* oils, Fitoterapia, 59, 141-144

Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M & Michel H, 1992, Hepatitis after germander (*Teucrium chamaedrys*) administration: Another instance of herbal medicine hepatotoxicity, Ann.Int.Med., 117, 129-132

Leathwood PD & Chauffard F, 1983, Quantifying the effects of mild sedatives, J.Psychiatr.Res., 17, 115-122

Leathwood PD & Chauffard F, 1985, Aqueous extract of valerian reduces latency to fall asleep in man, Planta Med., 51, 144-148

Leathwood PD, Chauffard F, Heck E & Munoz-Box R, 1982, Aqueous extract of valerian root improves sleep quality in man, Pharmacol.Biochem.Behav., 17, 65-71

Leathwood PD, Chauffard F & Munoz-Box R, 1983, Effect of *Valeriana officinalis* L. on subjective and objective sleep parameters *in* Sleep 1982, 6th Eur.Congr.Sleep Res., Zurich 1982. Basel: Karger, 402-405

Leukel A, Fricke U & Holz J, 1986, Studies on the activity of *Crataegus* compounds upon the isolated guinea pig heart, Planta Med., 52, 65

Leung AY, 1980, Encyclopedia of common natural ingredients used in food, drugs and cosmetics, New York-Chichester: Wiley

Lewis WH & Smith PR, 1979, Pokeroot herbal tea poisoning, JAMA, 242, 2759-2760

Lewith GT & Aldridge D (eds.), 1993, Clinical Research Methodology for Complementary Therapies, London: Hodder & Stoughton

Li Wan PO A, 1991, Evening primrose oil, Pharm.J., 246, 670-676

Lievre M, Andrieu J-L & Baconin A, 1985, Assessment in the anesthetized dog of the cardiovascular effects of a pure extract (hyperoside) from hawthorn, Ann.Pharm.Fr., 43, 471-477

Lim-Sylianco CY, Luistro A & Panizzares, 1977, Mutagenicity studies of aqueous extracts from leaves of comfrey (*Symphytum officinale* Linn.), NRCP Res.Bull., 32, 178-191

Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W & Melchart D, 1996, St. John's Wort for depression: An overview and meta-analysis of randomised clinical trials, Br.Med.J., 313, 253-258

Locock RA, 1985, Capsicum, Can.Pharm.J., 118, 517-519

Loeper J, Descatoire V, Letteron P, Moulis C, Degott C & Pessayre D, 1993, Mechanism for the hepatotoxicity of Germander (*Teucrium chamaedrys*), a plant responsible for an epidemic of hepatitis in France, J.Hepatol., 18 (Suppl.1): S74

Longiave D, Omini C, Nicosia S & Berti F, 1978, The mode of action of aescin on isolated veins: Relationship with PGF_2a, Pharmacol.Res.Comm., 10, 145-153

Luther P, Thiese H, Chatterjee B, Karduck D & Uhlenbruck G, 1980, The lectin from *Viscum album* L. - isolation, characterization, properties and structure, Int.J.Biochem., 11, 429-435

Lyford CL, Vergava GG & Moeller DD, 1976, Hepatic veno-occlusive disease originating in Ecuador, Gastroenterol., 70, 105-108

Mabey R (ed.), 1988, The complete new herbal, London: Elm Tree Books

MacGregor FB, Abernethy VE, Dahabra S, Cobden I & Hayes PC, 1989, Hepatotoxicity of herbal remedies, Br.Med.J., 299, 1156-1157

Madge M, 1996, An opportunity (letter), Pharm.J., 257, 305

Makheja AM & Bailey JM, 1981, The active principle in feverfew, Lancet, 2, 1054

Makheja AM & Bailey JM, 1982, A platelet phospholipase inhibitor from the medicinal herb feverfew (*Tanacetum parthenium*), Prostaglandins Leukot.Med., 8, 653-660

Mann C & Staba EJ, 1986, The Chemistry, Pharmacology, and Commercial Formulations of Chamomile *in* Herbs, Spices, and Medicinal Plants: Recent Advances in Botany, Horticulture, and Pharmacology, Volume 1 (eds. LE Craker & JE Simon), Arizona: Oryx Press, 235-280

Mantero F, 1981, Exogenous mineralocorticoid-like disorders, Clin.Endocrinol.Metab., 10, 465-478

Marshall JM, 1990, Aloe vera gel: What is the evidence?, Pharm.J., 244, 360-362

Massanet GM, Pando E, Rodriguez-Luis F & Zubia E, 1989, Lignans: A review, Fitoterapia, 60, 3-35

Mattocks AR, 1986, Chemistry and toxicology of pyrrolizidine alkaloids, London: Academic Press

Mazza G, 1985a, Gas chromatographic and mass spectrometric studies of the constituents of the rhizome of calamus I. The volatile constituents of the essential oil, J.Chromatogr., 328, 179-194

Mazza G, 1985b, Gas chromatographic and mass spectrometric studies of the constituents of the rhizome of calamus II. The volatile constituents of alcoholic extracts, J.Chromatogr., 328, 195-206

McCaleb RS, 1996, Recent developments in botanical health care in the USA. Presented at the INDENA workshop on "From act to actions when dealing with botanicals", Milan, September 9, 1996

McClure JW, 1975, Physiology and Functions of Flavonoids *in* The Flavonoids (eds. JB Harborne, TJ Mabry & H Mabry), London: Chapman & Hall

McCoig A, 1996, Need for controls, Pharm.J., 257, 198

McGee J, Patrick RS, Wood CB & Blumgart LH, 1976, A case of veno-occlusive disease of the liver in Britain associated with herbal tea consumption, J.Clin.Path., 29, 788-794

McHenry PM, Williams HC & Bingham EA, 1995, Management of atopic eczema, Br.Med.J., 310, 843-847

McLean EK, 1970, The toxic actions of pyrrolizidine (*Senecio*) alkaloids, Pharmacol.Rev., 22, 429-483

McPherson A, 1979, Pokeweed and other lymphocyte mitogens *in* Toxic Plants (ed. AD Kinghorn), New York: Columbia University Press, 84-102

Meier B, Sticher O & Julkunen-Tiitto R, 1988, Pharmaceutical aspects of the use of willows in herbal remedies, Planta Med., 54, 559-560

Menges LJ, 1994, Regular and alternative medicine: The state of affairs in the Netherlands, Soc.Sci.Med., 39, 871-873

Middleton E, 1988, Plant flavonoid effects on mammalian cell systems *in* Herbs, spices, and medicinal plants: Recent advances in botany, horticulture, and pharmacology, volume 3 (eds. LE Craker & JE Simon), Arizona: Oryx Press

Miller EC & Miller JA, 1979, Naturally occurring chemical carcinogens that may be present in foods *in* International Review of Biochemistry, Biochemistry of Nutrition 1A, 27, 123-161,
(eds. A Neuberger & Jukes TH), Baltimore: University Park Press

Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A & Miller JA, 1983, Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally

occurring and synthetic alkenylbenzene derivatives related to safrole and estragole, Cancer Res., 43, 1124-1132

Miller JA & Miller EC, 1983, The 1983 Walter Hubert Lecture: The metabolic activation and nucleic acid adducts of naturally-occurring carcinogens. Recent results with ethyl carbamate and the spice flavours safrole and estragole, Br.J.Cancer, 48, 1-15

Millet Y, 1980, Experimental study of the toxic convulsant properties of commercial preparations of essences of sage and hyssop, Electroencephal.Clin.Neurophysiol., 49, 102P

Mills S, 1985, The Dictionary of Modern Herbalism: A Comprehensive Guide to Practical Herbal Therapy, Wellingborough: Thornsons

Mills S, 1993, Herbal medicines: Research strategies *in* Clinical Research Methodology for Complementary Therapies (eds. GT Lewith & D Aldridge), London: Hodder & Stoughton, 394-407

Mitchell J & Rook A, 1979, Botanical dermatology - plants and plant products injurious to the skin, Vancouver: Greengrass

Mitchell-Heggs CAW, Conway M & Cassar J, 1990, Herbal medicine as a cause of combined lead and arsenic poisoning, Human & Experimental Toxicology, 9, 195-196

Mohabbat O, Srivastava RN, Younos MS, Sedig GG, Merzad AA & Aram GN, 1976, An outbreak of hepatic veno-occlusive disease in north-western Afghanistan, Lancet, 2, 269-271

Morelli I, 1983, Selected medicinal plants, Rome: FAO

Moore J, Phipps K, Marcer D & Lewith G, 1985, Why do people seek treatment by alternative medicine?, Br.Med.J., 290, 28-29

Morriset T, Cote NG, Panisset JC, Jemni L, Camirand P & Brodeur A, 1987, Evaluation of the healing activity of hydrocotyle tincture in the treatment of wounds, Phytotherapy Res., 1, 117-121

Morton JF, 1986, The potential carcinogenicity of herbal teas, Envir.Carcino.Revs. (J.Envir.Sci.Hlth.), C4, 203-223

Mostefa-Kara N, Pauwels A, Pines E, Biour M & Levy VG, 1992, Fatal hepatitis after herbal tea, Lancet, 340, 674

Mowrey DB & Clayson DE, 1982, Motion sickness, ginger, and psychophysics, Lancet, 1, 655-657

Murphy JJ, Heptinstall S & Mitchell JRA, 1988, Randomised double-blind placebo-controlled trial of feverfew in migraine prevention, Lancet, 2, 189-192

Murray J & Shepherd S, 1988, Alternative or additional medicine? A new dilemma for the doctor, J.R.Coll.Gen.Pract., 38, 511-514

Natarajan S & Paily PP, 1973, Effect of topical *Hydrocotyle asciatica* in psoriasis, Indian J.Dermatol., 18, 82-85

Newall CA, Anderson LA & Phillipson JD, 1996, Herbal Medicines: A Guide for Healthcare Professionals, London: The Pharmaceutical Press

Newton G, 1979, "Herbal" medicines and rheumatoid arthritis (letter), Br.Med.J., 2, 669

Nicholls P, 1992, Homoeopathy in Britain after the Mid-Nineteenth Century *in* Alternative Medicine in Britain (ed. M Saks), Oxford: Clarendon Press

O'Driscoll J, Burden AD & Kingston TP, 1992, Potent topical steroid obtained from a Chinese herbalist, Br.J.Dermatol., 127, 543-544

Offerhaus L, Dukes MNG & Smits HM, 1979, "Herbal" medicines and rheumatoid arthritis, Br.Med.J., 2, 668

Oliveto EP, 1972, Nordihydroguaiaretic acid. A naturally occurring antioxidant, Chem.Ind., 677-679

Olson T, 1974, The disulphide bonds of viscotoxin A2 from the European mistletoe (*Viscum album* L. Loranthaceae), Acta Pharm.Suec., 11, 381-386

Opdyke DLJ, 1974a, Pennyroyal oil european, Food Cosmet.Toxicol., 12, 949-950

Opdyke DLJ, 1974b, Safrole, Food Cosmet.Toxicol., 12, 983-986

Opdyke DLJ, 1974c, Rosemary Oil, Food Cosmet.Toxicol., 12, 977-978

Opdyke DLJ, 1976, Tansy oil, Food Cosmet.Toxicol., 14, 869-871

Opdyke DLJ, 1982, Sassafras oil, Food Cosmet.Toxicol., 20, 825-826

Pathak D, Pathak K & Singla AK, 1991, Flavonoids as medicinal agents: Recent advances, Fitoterapia, 62, 371-385

Pauli G, Bessot JC, Dietemann-Molard A, Braun PA & Thierry R, 1985, Celery sensitivity: Clinical and immunological correlations with pollen energy, Clin.Allergy, 15, 273-279

Penn RG, 1981, Adverse reactions to herbal preparations *in* Iatrogenic Diseases 2nd Edition Update (eds. PF D'Arcy & JP Griffin), Oxford: Oxford University Press, 205-217

Penn RG, 1982, Adverse reactions to herbal and other unorthodox medicines *in* Iatrogenic Diseases 2nd Edition Update (eds. PF D'Arcy & JP Griffin), Oxford: Oxford University Press, 196-200

Perfitt VD, 1996, British Herbal Medicine Association (BHMA) correspondence to members on proposed Code of Practice for Unlicensed Herbal Remedies, Gloucestershire: BHMA

Perharic L, Shaw D, Colbridge M, House I, Leon C & Murray V, 1994a, Toxicological problems resulting from exposure to traditional remedies and food supplements, Drug Safety, 11, 284-294

Perharic L, Shaw D & Murray V, 1994b, An appeal to pharmacists to report adverse effects of herbal and vitamin products, Pharm.J., 252, 479

Perharic-Walton L & Murray V, 1992, Toxicity of Chinese herbal remedies (letter), Lancet, 340, 673

Perkin MR, Pearcy RM & Fraser JS, 1994, A comparison of the attitudes shown by general practitioners, hospital doctors and medical students towards alternative medicine, J.R.Soc.Med., 87, 523-525

Petkov V, 1979, Plants with hypotensive, antiatheromatous and coronarodilatating action, Am.J.Chinese Med., 7, 197-236

Petry T, Bowden G, Buhler D & Sipes K, 1986, Genotoxicity of the pyrrolizidine alkaloid jacobine in rats, Toxicol.Lett., 32, 275-281

Phillipson JD, 1981, The pros and cons of herbal remedies, Pharm.J., 227, 387-392

Phillipson JD, 1990, Personal communication

Phillipson JD, 1992, Quality assurance of medicinal plants *in* First World Congress on medicinal and aromatic plants for human welfare, WOCMAP, quality, phytochemistry, industrial aspects, economic aspects (eds. Ch Franz, R Seitz & N Verlet). Acta Horticulturae 1993, 333, 117-122

Phillipson JD & Anderson LA, 1984a, Pharmacologically active compounds in herbal remedies, Pharm.J., 232, 41-44

Phillipson JD & Anderson LA, 1984b, Ginseng - quality, safety and efficacy?, Pharm.J., 232, 161-165

Phillipson JD & Anderson LA, 1984c, Herbal remedies used in sedative and antirheumatic preparations. Part 1., Pharm.J., 233, 80-82

Phillipson JD & Anderson LA, 1984d, Herbal remedies used in sedative and antirheumatic preparations. Part 2., Pharm.J., 233, 111-115

Phillipson JD & Anderson LA, 1984e, Counterprescribing of herbal remedies. Part 1., Pharm.J., 233, 235-238

Phillipson JD & Anderson LA, 1984f, Counterprescribing of herbal remedies. Part 2., Pharm.J., 233, 272-274

Phillipson JD & Anderson LA, 1986, Herbal medicines (letter), Pharm.J., 236, 289

Piette A-M, Bauer D & Chapman A, 1984, Hypokaliemie majeure avec rhabdomyolase secondaire a la ingestion de pastis non alcoolise, Ann.Med.Interne. (Paris), 135, 296-298

Pizzorno JE & Murray MT, 1985, A textbook of natural medicine, Seattle, WA: John Bastyr College Publications (looseleaf)

Platt S, 1996, Complementary Medicine, Pharmacy Magazine, February, 30-33

Pompei R, Pani A, Marcialis MA & Loddo B, 1980, Antiviral activity of glycyrrhizic acid, Experienta, 36, 304

Pontifex AH & Garg AK, 1985, Lead poisoning from an Asian Indian folk remedy, Can.Med.Assoc., 133, 1227-1228

Preininger V, 1975, The pharmacology and toxicology of Papaveraceae alkaloids *in* The Alkaloids XV, London: Academic Press (ed. RHF Manske), 207-261

Price KR, Johnson IT & Fenwick GR, 1987, The chemistry and biological significance of saponins in foods and feedingstuffs, CRC Critical Reviews in Food Science and Nutrition, 26, 27-135

Pusztai A, 1991, Plant Lectins *in* Chemistry and Pharmacology of Natural Products series (series eds. JD Phillipson, DC Ayres & H Baxter), Cambridge: Cambridge University Press

Racz-Kotilla E, Jozsa J & Racz G, 1980, Hypotensive and beta-blocking efect of procyanidins of *Crataegus monogyna*, Planta Med., 39, 239

Radford DJ, Gillies AD, Hinds JA & Duffy P, 1986, Naturally occurring cardiac glycosides, Med.J.Aust., 144, P540-544

Raman A & Houghton PJ, 1995, Ginseng, Pharm.J., 254, 150-151

Raman A & Jamal J, 1997, "Herbal" hayfever remedy found to contain conventional drugs, Pharm.J., 258, 105-106

Ramaswamy AS, Periyasamy SM & Basu N, 1970, Pharmacological studies on *Centella asciatica* Linn. (*Brahma manduki*) (N.O. Umbelliferae), J.Res.Indian Med., 4, 160-175

Ravokatra A & Ratsimamanga AR, 1974, Action of a pentacyclic triterpenoid, asiaticoside, obtained from *Hydrocotyle madagascariensis* or *Centella asciatica* against gastric ulcers of the Wistar rat exposed to cold (2^0), C.R.Acad.Sci. (Paris), 278, 1743-1746

Ravokatra A, Loiseau A, Ratsimamanga-Urverg S, Nigeon-Dureuil M & Ratsimamanga AR, 1974, Action of asiaticoside extracted from hydrocotyle on duodenal ulcers induced with mercaptoethylamine in male wistar rats, C.R.Acad.Sci. (Paris), 278, 2317-2321

Recio MC, Rios JL & Villar A, 1989, Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. Part II., Phytotherapy Res., 3, 77

Reiter MC & Brandt W, 1985, Relaxant effects on tracheal and ileal smooth muscles of the guinea pig, Arzneim-Forsch. , 35, 408-414

Reynolds JEF (ed.), 1982, Martindale: The Extra Pharmacopoeia, 28th edition, London: The Pharmaceutical Press

Reynolds JEF (ed.), 1996, Martindale: The Extra Pharmacopoeia, 31st edition, London: The Pharmaceutical Press

Ribes G, DaCosta C, Loubatieres-Mariani MM, Sauvaire Y & Baccon JC, 1987, Hypocholesterolaemic and hypotriglyceridaemic effects of subfractions from fenugreek seeds in alloxan diabetic dogs, Phytotherapy Res., 1, 38-42

Ridker PM, 1987, Toxic effects of herbal teas, Arch.Environ.Hlth., 42, 133-136

Ridker PM, Ohkuma S, McDermott WV, Trey C & Huxtable RJ, 1985, Hepatic veno-occlusive disease associated with the consumption of pyrrolizidine containing dietary supplements, Gastroenterol., 88, 1050-1054

Ries CA & Sahud MA, 1975, Agranulocytosis caused by Chinese herbal medicines, JAMA, 231, 352-355

Roberge R, Brader,E, Martin M, Jehle D, Evans T, Harchelroad F, Magreni G, Gesualdi G, Belardi C, Sayre M & Hartmann A, 1986, The root of evil - poke weed intoxication, Ann.Emerg.Med., 15, 470-473

Robinson T, 1986, The Biochemical Pharmacology of Plant Alkaloids *in* Herbs, Spices, and Medicinal plants: Recent Advances in Botany, Horticulture, and Pharmacology, Volume 1 (eds. LE Craker & JE Simon), Arizona: Oryx Press

Rodriguez E, Towers GHN & Mitchell JC, 1976, Review: Biological activities of sesquiterpene lactones, Phytochem., 15, 1573-1580

Roitman JN, 1981, Comfrey and liver damage (letter), Lancet, 1, 944

Rosell S & Samuelsson G, 1966, Effect of mistletoe viscotoxin and phoratoxin on blood circulation, Toxicon., 4, 107-110

Rothkopf M, Vogel G, Lang W & Leng E, 1977, Animal experiments on the question of the renal toleration of the horse chestnut saponin aescin, Arzneim-Forsch., 27, 598-605

Roulet M, Laurini R, Rivier L & Calame A, 1988, Hepatic veno-occlusive disease in newborn infant of woman drinking herbal tea, J.Pediatr., 112, 433-436

Routledge PA & Spriggs TLB, Atropine as possible contaminant of comfrey tea, Lancet, 1, 963-964

Rudofsky G, Neiss A, Otto K & Seibel K, 1986, Odemprotektive Wirkung und klinische Wirksamkeit von Rosskastaniensamenextrakt im Doppelblindversuch, Phlebol.Proktol., 15, 47-53

Ruggeri CS, Olivari G, Benvenuti ME, DeIacobis M, Peruzza M, Chinello M, Mazzolini GF & Rubini G, 1985, L. Carnetina cloruro e KCL nel trattamento di un caso di rabdomiolisi atraumatica senza mioglobinuria da ingestione di liquerizia, Minn.Med., 76, 725-728

Samuelsson G, 1974, Mistletoe toxins, Syst.Zool., 22, 566-569

Samuelsson G & Jayawardene AL, 1974, Isolation and characterization of viscotoxin 1-Ps from *Viscum album* L. ssp. *Austriacum* (Wiesb.) Vollmann, growing on *Pinus silvestris*, Acta Pharm.Suec., 11, 175-184

Saxena RC, 1985, Drug reactions with herbal drugs, Indian J.Pharmacol., 17, 165-169

Schmidt RJ, 1986, Compositae, Clinics in Dermatology, 4, 46-61

Scholz H, Kascha S & Zingerie H, 1980, Atropine poisoning: Case report, Fortschr.Med., 98, 1525-1526

Schwarting AE, 1977, Dimeric Natural Compounds with Pharmacological Activity *in* New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity (eds. H Wagner & P Wolff), Berlin: Springer-Verlag, 197-211

Seiber JN, Nelson CJ & Lee MS, 1982, Cardenolides in the latex and leaves of seven *Asclepias* species and *Calotropis procera*, Phytochem., 21, 2348-2348

Seiber JN, Lee, SM, McChesney MM, Watson TR, Nelson CJ & Brower LP, 1985, New cardiac glycosides (cardenolides) from *Asclepias* species, Plant Toxicol. Proceedings of the Aust/USA poisonous plants symposium, 427-437

Sekizawa J & Shibamoto T, 1982, Genotoxicity of safrole-related chemicals in microbial test systems, Mutat.Res., 101, 127-140

Shamma M, 1972, The Isoquinoline Alkaloids - Chemistry and Pharmacology, New York: Academic Press

Sharma RD, 1986, Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses in human subjects, Nutr.Res., 6, 1353-1364

Sharma U, 1992, Complementary Medicine Today: Practitioners and Patients, London: Tavistock/Routledge

Shaw D, Kolev S, Leon C, Bell G, Colbridge M & Murray V, 1996, Toxicological problems resulting from exposure to traditional medicines and food supplements, London: Ministry of Agriculture, Fisheries & Food (MAFF)

Shellard EJ, 1987, Medicines from plants with special reference to herbal products in Great Britain, Planta Med., 53, 121-123

Siegal RK, Elsohly MA, Plowman T,Rury PM & Jones RT, 1986, Cocaine in herbal tea, JAMA, 255, 40

Simanek V, 1985, Benzophenanthridine Alkaloids *in* The Alkaloids Vol. 26 (ed. A Brossi), Orlando: Academic Press

Simon JE, Chadwick AF & Craker LE, 1984, Herbs - an indexed bibliography 1971-1980, Oxford: Elsevier

Spigelblatt L, Laine-Ammara G, Pless B & Guyver A, 1994, The use of alternative medicine by children, Pediatrics, 94, 811-814

Srivastava KC, 1989, Effect of onion and ginger consumption on platelet thromboxane production in humans, Prostaglandins Leukot.Essent. Fatty Acids, 35, 183-185

Srivastava KC & Mustafa T, 1989, Ginger and rheumatic disorders, Med.Hypoth., 29, 25-28

Stahl E & Keller K, 1981, Zur Klassifizierung handelsublicher Kalmusdrogen, Planta Med., 43, 128-140

Stein H & Isaacson C, 1962, Veno-occlusive disease of the liver, Br.Med.J., 1, 372-374

Stenger A, Tarayre J-P, Carilla E, Delhon A, Charveron M, Morre M & Lauressergues H, 1982, Pharmacology and biochemistry of hexane extract of *Serenoa repens*, Gazz.Med.Fr., 89, 2041-2048

Stewart PM, Wallace AM, Valentino R, Burt D, Shackleton CHL & Edwards CRW, 1987, Mineralocorticoid activity of liquorice: 11-β-hydroxysteroid dehydrogenase deficiency comes of age, Lancet, 2, 821-824

Sticher O, 1977, Plant Mono-, Di- and Sesquiterpenoids with Pharmacological or Therapeutical Activity *in* New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity (eds. H Wagner & P Wolff), Berlin: Springer-Verlag, 139-176

Stillman AE, Huxtable RJ, Consroe P, Kohner P & Smith S, 1977, Hepatic venocclusive disease due to pyrrolizidine poisoning in Arizona, Gastroenterol., 73, 349-352

Stirpe F, Leff RF, Onyon LJ, Ziska P & Franz H, 1980, Inhibition of protein synthesis by a toxic lectin from *Viscum album* L. (mistletoe), Biochem.J., 190, 843-845

Stricht BIV, Parvais OE, Vanhaelen-Fastre R & Vanhaelen MH, 1994, Remedies may contain cocktail of active drugs, Br.Med.J., 308, 1162

Stuart KL & Bras G. 1957, Veno-Occlusive Disease of the Liver, Quarterly J.Med., 26, 291-315

Sullivan JB, Rumack BH, Thomas H, Peterson RG & Bryson P, 1979, Pennyroyal oil poisoning and hepatotoxicity, JAMA, 242, 2873

Sultan C, Terraza A, Devillier C, Carilla E, Briley M, Loire C & Descomps B, 1984, Inhibition of androgen metabolism and binding by a liposterolic extract of "*Serenoa repens* B" in human foreskin fibroblasts, J.Steroid Biochem., 20, 515-519

Suzuki O, Katsumata Y, Oya M, Bladt S & Wagner H, 1984, Inhibition of monoamine oxidase by hypericin, Planta Med., 50, 272-274

Swanson AB, Chambliss DD, Blomquist JC, Miller EC & Miller JA, 1979, The mutagenicities of safrole, estragole, eugenol, *trans*-anethole, and some of their known or possible metabolites for *Salmonella typhimurium* mutants, Mutat.Res., 60, 143-153

Szelenyi I, Isaac O & Thiemer K, 1979, Pharmacologocal experiments with compounds of chamomile III. Experimental studies of the ulcerprotective effect of chamomile, Planta Med., 35, 218-227

Taddei I, Giachetti D, Taddei E & Mantovani, 1988, Spasmolytic activity of Peppermint, Sage and Rosemary essences and their major constituents, Fitoterapia, 59, 463-468

Tamaya MD, Sato S & Okado HH, 1986, Possible mechanism of steroid action of the plant herb extracts glycyrrhizin, glycyrrhetinic acid, and paeoniflorin: Inhibition by plant herb extracts of steroid protein binding in the rabbit, Am.J.Obstet.Gynecol., 155, 1134-1139

Tandon BW, Tandon RK, Tandon HD & Narndranathan M, 1976, An epidemic of veno-occlusive disease of the liver in Central India, Lancet, 2, 271-272

Tasca A, Barulli M, Cavazzana A, Zattoni F, Artibani W & Pagano F, 1985, Treatment of obstruction in prostatic adenoma using an extract of *Serenoa repens*. Double-blind clinical test v. placebo, Minn.Urol.Nefrol., 37, 87-91

Tay C-H & Seah C-S, 1975, Arsenic poisoning from anti-asthmatic herbal preparation, Med.J.Aust., 2, 424-428

Taylor-Reilly D, 1983, Young doctors' views on alternative medicine, Br.Med.J., 287, 337-339

Taylor JM, Jones WI, Hagan EC, Gross MA, Davis DA & Cook EL, 1967, Toxicity of oil of calamus (Jammu variety), Tox. & Appl.Pharmacol., 10, 405

Teuber M & Schmalreck AF, 1973, Membrane leakage in *Bacillus subtillus* 168 induced by the hop constituents lupulone, humulone, isohumulone and humulinic acid, Arch.Mikrobiol., 94, 159-171

Thomas KJ, Carr J, Westlake L & Williams B, 1991, Use of non-orthodox and conventional health care in Great Britain, Br.Med.J., 302, 207-210

Thompson EB, Aynilian GH, Gora P & Farnsworth NR, 1974, Preliminary study of potential antiarrhythmic effects of *Crataegus monogyna*, J.Pharm.Sci., 63, 1936-1937

Tidy PJL, 1996, Shopkeepers in white coats, Pharm.J., 257, 337

Tisserand R & Balacs T, 1995, Essential oil safety, Edinburgh: Churchill Livingstone

To LP, Hunt TP & Andersen ME, 1982, Mutagenicity of *trans*-anethole, estragole, eugenol and safrole in the Ames *Salmonella typhimurium* assay, Bull.Environm.Contam.Toxicol., 28, 647-654

Turner S & Mills S, 1993, A double-blind clinical trial on a herbal remedy for pre-menstrual syndrome; a case study, Complementary Therapies in Medicine, 1, 73-77

Tyler VE, Brady LR & Robbers J, 1981, Pokeroot *in* Pharmacognosy 8th edition, Philadelphia: Lea and Febiger, 493-494

Tyler VE, 1993, The Honest Herbal, 3rd edition, Philadelphia: Strickley

Vallance WB, 1955, Pennyroyal poisoning. A fatal case, Lancet, 2, 850-851

Vanhaelen M, Vanhaelen-Fastre R, But P & Vennerwegnem JL, 1994, Identification of aristolochic acid in Chinese herbs, Lancet, 343, 174

Vanherweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadoul M, Richard C, Vandervelde D, Verbeelen D, Vanhaelen-Fastre R & Vanhaelen M, 1993, Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs, Lancet, 341, 387-391

Vecchio P, 1994, Attitudes to alternative medicine by rheumatology outpatient attenders, J.Rheumatol., 21, 145-147

Visser GJ, Peters L & Rasker JJ, 1992, Rheumatologists and their patients seek alternative care: An agreement to disagree, Br.J.Rheumatol., 31, 485-490

Vogel G, Marek M-L & Oertner R, 1970, Untersuchungen zum Mechanismus der therapeutischen und toxischen Wirkung des Rosskastanien-saponins aescin, Arzneim-Forsch., 20, 699-705

Vorberg G, 1985, *Ginkgo biloba* extract (GBE): A long term study on chronic cerebral insufficiency in geriatric patients, Clin.Trials J., 22, 149-157

Wagner H, Bladt S & Zgainski EM, 1983, Plant drug analysis, Berlin: Springer-Verlag

Wagner H, 1987, Immunostimulants from higher plants (recent advances) *in* Biologically Active Natural Products (eds. K.Hostettmann & PJ Lea), Oxford: Clarendon Press, 127-141

Wall ME & Wani MC, 1995, Taxol *in* Alkaloids: Chemical and Biological Perspectives vol. 9 (ed. SW Pelletier), Oxford: Elsevier Science Ltd.

Wardwell WJ, 1994, Alternative medicine in the United States, Soc.Sci.Med., 38, 1061-1068

Wasner CK, 1984, Patients, physicians and unproven remedies, Clinical & Experimental Rheumatology, 2, 93-96

Westendorf J, 1982, Carito^{R} - *in vitro* Untersuchungen zum Nachweiss spasmolytischer und kontraktiler Einflusse, Therapiewoche, 32, 6291-6297

Weston CFM, Cooper BT, Davies JD & Levine DF, 1987, Veno-occlusive disease of the liver secondary to ingestion of comfrey, Br.Med.J., 295, 183

Wharton R & Lewith G, 1986, Complementary medicine and the general practitioner, Br.Med.J., 292, 1498-1500

Williams CA, Hoult JRS, Harborne JB, Greenham J & Eagles J, 1995, A biologically active lipophilic flavonol from *Tanacetum parthenium*, Phytochem., 38, 267-270

Wiseman RW, Miller EC, Miller JA & Liem A, 1987, Structure-activity studies of the hepatocarcinogenicities of alkenylbenzene derivatives related to estragole and safrole on administration to prewean ing male C57BL/6J mice, Cancer Res., 47, 2275-2283

Wood CD, Manno JE, Wood MJ, Manno BR, & Mims ME, 1988, Comparison of efficacy of ginger with various antimotion sickness drugs, Clin.Res.Pract.Drug Reg.Affairs, 6, 129-136

Yu H, Zhong S, Chan K & Berry M, 1995, Pharmacognostical investigations on traditional Chinese medicinal herbs: Identification of four herbs from the UK market, J.Pharm.Pharmacol., 47, 1129

Zaynoun S, Abi LA, Tenekjian K & Kurban A, 1985, The bergapten content of garden parsley and its significance in causing cutaneous photosensitisation, Clin.Exp.Dermatol., 10, 328-331

Zhang X, 1996, Regulation and registration of herbal medicines. Presented at the 32nd annual meeting, self-medication in Europe - Enlarging the horizon, European Proprietary Medicines Manufacturing Association, Istanbul: 29 May - 1 June

Ziska P, Franz H & Kindt A, 1978, The lectin from *Viscum album* L. purification by biospecific affinity chromatography, Experientia, 34, 123-124

Ziska P, Eifler R & Franz H, 1979, Chemical modification studies on the D-galactopyranosyl binding lectin from the mistletoe *Viscum album* L., Acta Biol.Med.Ger., 38, 1361-1363

9. APPENDIXES

Appendixes 1-20 from Newall et al, 1996.

APPENDIX 1 Potential Drug/Herb Interactions

Very few herbal interactions have been reported in the medical literature, but the following **potential** drug/herb interactions are listed on the basis of known herbal constituents and their reported pharmacological actions. It should be emphasised that many drug interactions are harmless and many of those that are potentially harmful occur only in a small proportion of patients and may then vary in severity from patient to patient. Health-care professionals should be alert to undeclared use of herbal remedies as a possible cause of unexplained toxicity or lack of effect of conventional medicines.

Suspected herb/drug interactions should be reported to the regulatory authorities, as for any other suspected adverse reaction to drugs or herbs, whether licensed or not.

Drug/ Therapeutic Category Affected	*Herbal Ingredients Interacting*	*Possible Effects*
Gastrointestinal System		
Antacids, ulcer-healing drugs	Herbal ingredients irritant to gastrointestinal tract. See appendix 13	Exacerbation of symptoms Risk of systemic side-effects
Antidiarrhoeal drugs	Herbal ingredients with laxative activity. See appendix 2	Antagonism
Laxatives	Herbal ingredients with laxative activity. See appendix 2	Potentiation; increased risk of side-effects
Cardiovascular system		
Cardiac glycosides	Cardioactive herbal ingredients. See appendix 3	Potentiation; increased risk of side-effects
Diuretics	Herbal ingredientswith diuretic activity. See appendix 4 Herbal ingredients with hypotensive activity. See appendix 5	Potentiation; increased risk of hypokalaemia Difficulty in controlling diuresis; hypertension
Anti-arrhythmic activity	Cardioactive herbal ingredients. See appendix 3 Herbal ingredients with diuretic activity. See appendix 4	Interference/antagonism with existing therapy Antagonism if hypokalaemia occurs
Beta-adrenoceptor blocking drugs	Cardioactive herbal ingredients. See appendix 3 Herbal ingredients with significant levels of amines/ sympathomimetic activity. See appendix 14	Potential antagonism Potential risk of severe hypertension
Antihypertensive therapy	Herbal ingredients with hypertensive activity. See appendix 5 Herbal ingredients with mineralocorticoid activity, e.g. bayberry, liquorice. See appendix 10 Herbal ingredients with hypotensive activity. See appendix 5 Herbal ingredients with significant levels of amines/sympathomimetic activity. See appendix 14 Herbal ingredients with diuretic activity. See appendix 4	Antagonism Antagonism Potentiation Antagonism Risk of potentiation/ interference with existing therapy
Lipid-lowering drugs	Herbal ingredients with hypolipidaemic activity. See appendix 7	Additive effect

APPENDIX I Potential Drug/Herb Interactions

Drug/ Therapeutic Category Affected	*Herbal Ingredients Interacting*	*Possible Effects*
Cardiovascular System (*continued*)		
Nitrates and calcium-channel blockers	Cardioactive ingredients. See appendix 3	Interference with therapy
	Blue cohosh	Interference with therapy
	Herbal ingredients with hypertensive activity. See appendix 5	Antagonism
	Herbal ingredients with anticholinergic activity	Reduced sublingual absorption of glyceryl trinitrate
Sympathomimetics	Herbal ingredients with significant sympathomimetic amines. See appendix 14	Potentiation: increased risk of hypertension
	Herbal ingredients with hypertensive activity. See appendix 5	Increased risk of hypertension
	Herbal ingredients with hypotensive activity. See appendix 5	Antagonism
Anticoagulants	Herbal ingredients with coagulant/ anticoagulant activity. See appendix6	Risk of potentiation or antagonism
	Herbal ingredients with coumarins. See appendix 15	Risk of potentiation
	Herbal ingredients with significant salicylate levels. See appendix 6	Risk of potentiation
	Garlic	Raised INR reported in 2 patients receiving warfarin
	Horse-chestnut	Plasma protein binding
Respiratory System	Herbal ingredients that are potentially allergenic. See appendix 12	Risk of allergic reaction
Terfenadine	Cardioactive herbal ingredients. See appendix 3	May increase arrhythmogenic potential of terfenadine
	Herbal ingredients with diuretic activity. See appendix 4	Electrolyte imbalance may increase arrhythmogenic potential of terfenadine
Allergic disorders	Herbal ingredients claimed to have sedative activity. See appendix 8	Potentiation of drowsiness associated with antihistamines
Central Nervous System		
Hypnotics and anxiolytics	Herbal ingredients claimed to have sedative activity. See appendix 8	Potentiation
Stimulants	Ginseng	Increased risk of ginseng side-effects
Antipsychotics	Herbal ingredients with diuretic activity. See appendix 4	Potentiation of lithium therapy; increased risk of toxicity; diuretics reported to reduce lithium clearance
	Herbal ingredients with anticholinergic activity	Risk of interference with therapy; anticholinergic drug reported to reduce plasma-phenothiazine concentrations
	Evening Primrose	Potential risk of seizure
Antidepressants	Herbal ingredients with sympathomimetic amines. See appendix 14	Risk of hypertensive crisis with monoamine-oxidase inhibitors (MAOIs)
	Ginseng	Suspected phenelzine interaction
	Herbal ingredients containing tryptophan.	Risk of CNS excitation and confusional states with MAOIs
	White Horehound	Hydroxytryptamine antagonism, *in vivo*
	Herbal ingredients with sedative activity. See appendix 8	May potentiate sedative side-effects
	Hops	Antagonism: contra-indicated in patients with depressive illness
	St. John's Wort	

Drug/ Therapeutic Category Affected	*Herbal Ingredients Interacting*	*Possible Effects*
Central Nervous System *(continued)*		
Drugs used in nausea and vertigo	Herbal ingredients with sedative activity. See appendix 8	May potentiate sedative side-effects
	Herbal ingredients with anticholinergic activity	Antagonism
Analgesics	Herbal ingredients with diuretic activity. See appendix 4	Increased risk of toxicity with anti-inflammatory analgesics
	Herbal ingredients with corticosteroid activity, e.g. bayberry, liquorice. See appendix 10	Possible reduction in plasma-aspirin concentrations
	Herbal ingredients with sedative activity. See appendix 8	May potentiate sedative side-effects
Antiepileptics	Herbal ingredients with sedative activity. See appendix 8	May potentiate sedative side-effects
	Borage	May increase risk of seizure
	Evening primrose oil	May increase risk of seizure
	Ground ivy	May increase risk of seizure
	Sage	May increase risk of seizure
	Herbal ingredients with significant salicylate levels (Meadowsweet, Poplar, Willow)	Transient potentiation of phenytoin therapy may occur
	Herbal ingredients with significant folic acid levels	Plasma-phenytoin concentration may be reduced
Drugs for parkinsonism	Herbal ingredients with anticholinergic activity	Potentiation: increased risk of side-effects
	Herbal ingredients with cholinergic activity	Antagonism
Infections		
Antifungal drugs	Herbal ingredients with anticholinergic activity	Risk of reduced absorption of ketoconazole
Endocrine System		
Antidiabetics	Herbal ingredients with hypo- or hyperglycaemic activity. See appendix 7	Potentiation/ antagonism of activity
	Herbal ingredientswith diuretic activity. See appendix 4	Antagonism
Drugs for hypo- and hyperthyroidism	Herbal ingredients with significant iodine content e.g. Fucus	Interference with therapy
	Horseradish, Myrrh	Interference with therapy
Corticosteroids	Herbal ingredients with diuretic activity. See Appendix 4	Risk of increased potassium loss
	Herbal ingredients with corticosteroid activity e.g. Bayberry, Liquorice. See appendix10	Increased risk of side-effects e.g. water and sodium retention
Sex hormones	Herbal ingredients with hormonal activity. See appendix 10	Possible interaction with existing therapy
Obstetrics and Gynaecology		
Oral contraceptives	Herbal ingredients with hormonal activity. See appendix 10	Possible interaction with existing therapy; may reduce effectiveness of oral contraceptive

APPENDIX 1 Potential Drug/Herb Interactions

Drug/ Therapeutic Category Affected	*Herbal Ingredients Interacting*	*Possible Effects*
Malignant Disease and Immunosuppression		
Methotrexate	Herbal ingredients with significant salicylate levels. See appendix 7	Increased risk of toxicity
Drugs affecting immune response	Herbal ingredients with immunostimulant activity. See appendix 11	Potentiation or antagonism
Musculoskeletal and Joint Diseases		
Systemic lupus erythematosus	Alfalfa	Antagonism: contra-indicated
Probenecid	Herbal ingredients with significant salicylate levels. See appendix 6	Risk of inhibition of probenecid
Eye		
Acetazolamide	Herbal ingredients with significant salicylate levels. See appendix 6	Increased risk of toxicity
Skin	Herbal ingredients with potential allergenic activity. See appendix 12 Herbal ingredients with phototoxic activity. See appendix 12	Allergic reaction: exacerbation of existing symptoms Phototoxic reaction: exacerbation of existing symptoms
Anaesthetics		
General anaesthetics	Herbal ingredients with hypotensive activity. See appendix 5	Potentiation of hypotensive effect
Competitive muscle relaxants	Herbal ingredients with diuretic activity. See appendix 4	Risk of potentiation if hypokalaemia occurs
Depolarising muscle relaxants	Cardioactive herbal ingredients. See appendix 3	Risk of arrhythmias

APPENDIX 2 Laxative Herbal Ingredients

Drug	*Effect*
Aloes	Anthraquinone constituents
Cascara	Anthraquinone constituents
Eyebright	Iridoids, *in vivo*
Frangula	Anthraquinone constituents
Horehound, White	Large doses
Ispaghula	Bulk laxative
Plantain	Iridoids, *in vivo* (much less than senna)
Rhubarb	Anthraquinone constituents
Senna	Anthraquinone constituents
Yellow Dock	Anthraquinone constituents

APPENDIX 3 Cardioactive Herbal Ingredients

Drug	*Effect*
Broom	Alkaloid constituents: cardiac depressant activity
Calamus	Antiarrhythmic activity
Cereus	Tyramine: cardiotonic amine
Cola	Caffeine
Coltsfoot	Cardiac calcium-channel blocking activity
Devil's Claw	Activity *in vivo*
Fenugreek	Activity *in vitro*
Figwort	Cardioactive glycoside constituents, activity *in vitro*
Fumitory	Alkaloid constituent: cardioactive
Ginger	Activity *in vivo*

Drug	*Effect*
Ginseng, Panax	Activity *in vivo*
Golden Seal	Berberine: cardioactive alkaloid
Hawthorn	Tyramine: cardiotonic amine; activity *in vivo*
Horehound, White	Activity *in vivo*
Lime Flower	Activity reputed with excessive ingestion
Maté	Caffeine
Mistletoe	Viscotoxin, negative inotropic effect
Motherwort	Cardiac glycoside constituents: activity *in vitro*
Parsley	Apiole poisoning, high doses
Pleurisy Root	Cardenolides, active *in vitro* and *in vivo*
Prickly Ash, Northern	Interaction with Na^+K^- ATPase
Prickly Ash, Southern	Interaction with Na^+K^- ATPase
Quassia	Activity *in vitro*
Shepherd's Purse	Activity *in vitro*
Squill	Cardiac glycoside constituents
Wild Carrot	Depressant activity *in vivo*

APPENDIX 4 Diuretic Herbal Ingredients

Drug	*Effect*
Agrimony	Activity *in vivo*
Artichoke	Reputed action
Boldo	Irritant oil
Broom	Reputed action
Buchu	Reputed action
Burdock	Reputed action
Celery	Reputed action
Cornsilk	Human activity
Couchgrass	Activity *in vivo*
Dandelion	Activity *in vivo*
Elder	Activity *in vivo*
Guaiacum	Reputed action
Juniper	Reputed action; terpinen-4-ol
Pokeroot	Activity *in vivo*
Shepherd's Purse	Activity *in vivo*
Squill	Activity *in vivo*
Uva Ursi	Reputed action
Yarrow	Activity *in vivo*

APPENDIX 5 Hypotensive and Hypertensive Herbal Ingredients

Drug	*Effect*
Hypotensive	
Agrimony	Hypotensive, *in vivo*
Asafoetida	Hypotensive, *in vivo*
Avens	Hypotensive, *in vivo*
Calamus	Hypotensive, *in vivo*
Celery	Hypotensive, human and *in vivo*
Cohosh, Black	Hypotensive, human
Cornsilk	Hypotensive, *in vivo*
Cowslip	Hypotensive, then hypertensive *in vivo*
Devil's Claw	Hypotensive, *in vivo*
Elecampane	Hypotensive, *in vivo*
Fenugreek	Hypotensive
Fucus	Hypotensive
Fumitory	Hypotensive, *in vivo*
Garlic	Hypotensive, *in vivo*
Ginger	Hypotensive
Ginseng, Panax	Hypotensive, human and *in vivo*
Goldenseal	Hypotensive, alkaloid effect
Hawthorn	Hypotensive, *in vivo*
Horehound, White	Vasodilator, oil
Horseradish	Hypotensive, *in vivo*
Mistletoe	Hypotensive, *in vivo*
Nettle	Hypotensive, *in vivo*
Parsley	Hypotensive, *in vivo*
Plantain	Hypotensive, *in vivo*
Pokeroot	Hypotensive, *in vivo*
Prickly Ash, Northern	Hypotensive, *in vivo*
Prickly Ash, Southern	Hypotensive, *in vivo*
Sage	Hypotensive
Shepherd's Purse	Hypotensive
Squill	Vasodilator, *in vivo*
St John's Wort	Hypotensive, *in vivo*
Vervain	Hypotensive
Wild Carrot	Hypotensive, *in vivo*
Yarrow	Hypotensive, *in vivo*

Drug	*Effect*
Hypertensive	
Bayberry	Hypertensive, myricitrin mineralocorticoid side-effect
Broom	Hypertensive, alkaloid effect, stated to be contra-indicated in hypertensive individuals
Capsicum	Hypertensive, increased catecholamine secretion
Cohosh, Blue	Hypertensive, methylcytisine has nicotinic action, alkaloid effect
Cola	Hypertensive, caffeine
Coltsfoot	Hypertensive, pressor activity
Gentian	Stated to be contra-indicated in hypertensive individuals
Ginger	Hypertensive
Ginseng, Panax	Hypertensive, human and *in vivo*
Liquorice	Hypertensive, mineralocorticoid side-effect
Maté	Hypertensive, caffeine
Vervain	Hypertensive

APPENDIX 6 Anticoagulant and Coagulant Herbal Ingredients

Drug	*Effect*
Anticoagulants	
Alfalfa	Coumarin constituents
Angelica	Coumarin constituents
Aniseed	Coumarin constituents
Arnica	Coumarin constituents
Asafoetida	Coumarin constituents, anticoagulant *in vivo*
Celery	Coumarin constituents
Chamomile, German	Coumarin constituents
Chamomile, Roman	Coumarin constituents
Clove	Eugenol powerful inhibitor of platelet activity
Fenugreek	Coumarin constituents
Feverfew	Inhibits platelet aggregation
Fucus	Anticoagulant action
Garlic	Interaction with warfarin reported
Ginger	Inhibition of platelet activity
Ginseng, Panax	Reduction of blood coagulation
Horse-chestnut	Coumarin constituents
Horseradish	Peroxidase stimulates synthesis of arachidonic acid metabolites
Liquorice	Inhibition of platelet activity
Meadowsweet	Salicylate constituents
Poplar	Salicylate constituents
Prickly Ash, Northern	Coumarin constituents
Prickly Ash, Southern	Coumarin constituents
Quassia	Coumarin constituents
Red Clover	Coumarin constituents
Willow	Salicylate constituents
Coagulants	
Agrimony	Coagulant, human
Goldenseal	Heparin antagonist
Mistletoe	Lectins, agglutinating activity
Yarrow	Coagulant, *in vivo*

APPENDIX 7 Hypolipidaemic and Hyperlipidaemic Herbal Ingredients

Drug	*Effect*
Alfalfa	Hypocholesterolaemic, *in vivo*
Artichoke	Hypocholesterolaemic, *in vivo*
Cohosh, Black	Hypocholesterolaemic, *in vivo*
Fenugreek	Hypocholesterolaemic, *in vivo*, human
Garlic	Hypocholesterolaemic, *in vivo*, human
Ginger	Hypocholesterolaemic, *in vivo*
Hydrocotyle	*Hyper*cholesterolaemic, *in vivo*
Plantain	Hypocholesterolaemic, *in vivo*
Scullcap	Hypocholesterolaemic, *in vivo*
Tansy	Hypocholesterolaemic, *in vivo*

APPENDIX 8 Sedative Herbal Ingredients

Drug	*Effect*
Calamus	Potentiation barbiturate sleeping time
Celery	*In vivo*
Chamomile, German	Human
Couchgrass	*In vivo*
Elecampane	*In vivo*
Ginsengs	CNS depressant and stimulant
Goldenseal	*In vivo*
Hops	*In vivo*
Hydrocotyle	*In vivo*
Jamaica Dogwood	*In vivo*
Nettle	CNS depression, *in vivo*
Passionflower	*In vivo*
Sage	*In vivo*
Scullcap	Reputed action
Shepherd's Purse	Potentiation barbiturate sleeping time
St John's Wort	Traditional use, bioflavonoids
Valerian	Human, *in vivo*
Wild Carrot	*In vivo*
Wild Lettuce	*In vivo*, related species

APPENDIX 9 Hypoglycaemic and Hyperglycaemic Herbal Ingredients

Drug	*Effect*
Hypoglycaemic	
Alfalfa	Hypoglycaemic, manganese, human
Aloes/ Aloe vera	Hypoglycaemic, *in vivo*
Burdock	Hypoglycaemic, *in vivo*
Celery	Hypoglycaemic, *in vivo*
Cornsilk	Hypoglycaemic, *in vivo*
Damiana	Hypoglycaemic
Elecampane	Hypoglycaemic
Eucalyptus	Hypoglycaemic, *in vivo*
Fenugreek	Hypoglycaemic, human
Garlic	Hypoglycaemic, *in vivo*, human
Ginger	Hypoglycaemic, *in vivo*

Drug	*Effect*
Ginseng, Panax	Hypoglycaemic
Juniper	Hypoglycaemic *in vivo*
Marshmallow	Hypoglycaemic
Myrrh	Hypoglycaemic
Nettle	Hypoglycaemic
Sage	Hypoglycaemic, *in vivo*
Tansy	Hypoglycaemic, *in vivo*
Hyperglycaemic	
Devil's Claw	Stated to be contra-indicated in diabetics
Elecampane	Hyperglycaemic
Figwort	*See* Devil's Claw: similar constituents
Ginseng, Panax	Hyperglycaemic
Hydrocotyle	Hyperglycaemic, human
Liquorice	Reduced K^+ aggravates glucose tolerance

APPENDIX 10 Hormonally Active Herbal Ingredients

Drug	*Effect*
Agnus Castus	Many uses in hormonal imbalance disorders
Alfalfa	Oestrogenic, *in vivo*
Aniseed	Oestrogenic
Bayberry	Mineralocorticoid
Cohosh, Black	Oestrogenic
Fucus	Hyper-/hypothyroidism reported
Ginsengs	Oestrogenic, human
Horseradish	May depress thyroid activity
Liquorice	Mineralocorticoid activity, human; oestrogenic *in vivo*, *in vitro*
Motherwort	Oxytocic
Pleurisy Root	Oestrogenic
Red Clover	Oestrogenic *in vivo*
Saw Palmetto	Oestrogenic and anti-androgenic *in vivo*; human use in prostate cancer
Vervain	Inhibition of gonadotrophic activity
Wild Carrot	Oestrogenic

APPENDIX 11 Immunostimulating Herbal Ingredients

Drug	*Effects*
Boneset	Stimulant *in vitro*
Calendula	Stimulant *in vitro*
Drosera	Stimulant and depressant (*in vitro*)
Echinacea	Stimulant *in vitro, in vivo*
Ginseng, Eleutherococcus	Stimulant, animal, human
Mistletoe	Stimulant, animal, human; suppressant (high doses), human
Saw Palmetto	Stimulant, *in vivo*

APPENDIX 12 Allergenic Herbal Ingredients

Drug	*Effect*
Agnus Castus	Allergic effects reported
Angelica	Furanocoumarins, photosensitivity, contact allergy
Aniseed	Furanocoumarins, photosensitivity, contact allergy
Apricot	Contact allergy, kernels
Arnica	Contact allergy
Artichoke	Sesquiterpene lactone constituents
Asafoetida	Irritant gum, contact allergy
Boneset	Sesquiterpene lactone constituents
Cassia	Allergic reactions, mainly contact
Celery	Furanocoumarins, photosensitivity
Chamomile, German	Sesquiterpene lactone constituents
Chamomile, Roman	Sesquiterpene lactone constituents
Cinnamon	Contact allergy
Cornsilk	Allergic reactions
Cowslip	Allergic reactions
Dandelion	Sesquiterpene lactone constituents
Elecampane	Sesquiterpene lactone constituents
Euphorbia	Histamine potentiating properties
Feverfew	Sesquiterpene lactone constituents
Fucus	Iodine may aggravate/trigger acne
Garlic	Sulphur-containing compounds, allergic reaction
Gravel Root	Sesquiterpene lactone constituents
Guaicum	Irritant resin
Holy Thistle	Sesquiterpene lactone constituents
Hops	Contact allergy
Hydrangea	Contact allergy
Hydrocotyle	Photosensitivity
Juniper	Contact allergy
Lady's Slipper	Contact allergy
Meadowsweet	Potentiation of histamine bronchospastic properties
Motherwort	Dermatitis, photosensitisation
Parsley	Furanocoumarins, photosensitivity
Pilewort	Contact allergy
Plantain	Contact allergy
Pleurisy Root	Contact allergy
Pulsatilla	Contact allergy, protoanemonin
Rosemary	Dermatitis, photosensitisation
St John's Wort	Photodermatitis, hypericin
Tansy	Sesquiterpene lactone constituents
Wild Carrot	Furanocoumarins, photosensitivity
Yarrow	Sesquiterpene lactone constituents

APPENDIX 13 Irritant Herbal Ingredients

Drug	*Effects*
Alfalfa	Irritant, canavanine in seeds
Arnica	Irritant to mucous membranes
Asafoetida	Irritant gum
Blue Flag	Irritant gum and oil
Bogbean	Irritant to GI tract
Boldo	Irritant oil
Buchu	Irritant oil
Capsicum	Capsaicinoids, mucosal irritants
Cassia	Irritant to mucous membranes, oil
Cinnamon	Irritant to mucous membranes, oil
Cohosh, Blue	Irritant to mucous membranes; spasmogenic *in vitro*
Cowslip	Irritant saponins
Drosera	Plumbagin, irritant
Eucalyptus	Irritant oil
False Unicorn	Large doses may cause vomiting
Figwort	Purgative effect
Garlic	Raw clove
Ground Ivy	Irritant oil
Guaiacum	Avoid if inflammatory condition

Drug	*Effects*
Horse-chestnut	Saponin constituents, contra-indicated in existing renal disease
Horseradish	Irritant oil
Hydrangea	May cause gastro-enteritis, hydrangin
Jamaica Dog-wood	Irritant to humans
Juniper	Irritant oil
Lemon Verbena	Irritant oil
Lime Flower	Irritant to kidney, oil
Nettle	Tea irritant to stomach
Parsley	Irritant oil
Pennyroyal	Toxic and irritant oil
Pilewort	Irritant sap
Pleurisy Root	Gastro-intestinal irritant
Pokeroot	Irritant saponins
Pulsatilla	Irritant to mucous membranes
Queen's Delight	Diterpene constituents
Sarsaparilla	Saponins
Senega	Saponins
Skunk Cabbage	Inflammatory and blistering to skin
Squill	Saponins

APPENDIX 14 Herbal Ingredients with Amines, Alkaloids or Sympathomimetic Action

Drug	*Effects*
Agnus Castus	alkaloids
Alfalfa	alkaloids
Aniseed	anethole, sympathomimetic
Arnica	betaines, choline
Bloodroot	alkaloids
Bogbean	alkaloids
Boldo	alkaloids
Borage	alkaloids
Broom	alkaloids, amines
Calamus	amines
Capsicum	sympathomimetic
Centaury	alkaloids
Cereus	tyramine
Cohosh, Black	alkaloids
Cohosh, Blue	alkaloids
Cola	alkaloids
Coltsfoot	alkaloids
Comfrey	alkaloids
Cornsilk	amines
Echinacea	alkaloids
Eyebright	alkaloids
Fenugreek	choline, trigonelline
Fumitory	alkaloids
Gentian	alkaloids
Ginseng, Panax	MAOI potentiation, suspected phenelzine interaction
Golden Seal	alkaloids
Gravel Root	alkaloids
Hawthorn	tyramine
Horehound, White	alkaloids
Hydrocotyle	alkaloids
Ispaghula	alkaloids
Jamaica Dog-wood	alkaloids
Liferoot	alkaloids
Lobelia	alkaloids
Maté	alkaloids, amines
Mistletoe	histamine release
Motherwort	alkaloids
Nettle	choline
Parsley	myristicin, sympathomimetic
Passionflower	alkaloids, MAOI activity
Plantain	alkaloids
Pleurisy Root	sympathomimetic
Pokeroot	betalains
Prickly Ash, Northern	alkaloids
Prickly Ash, Southern	alkaloids
Quassia	alkaloids
Sassafras	alkaloids
Shepherd's Purse	choline, tyramine
Skunk Cabbage	alkaloids
St. John's Wort	MAOI activity, *in vitro*
Stone Root	alkaloids
Valerian	alkaloids
Vervain	sympathomimetic
Yarrow	betonicine, stachydrine, betaine

APPENDIX 15 Herbal Ingredients containing Coumarins

Alfalfa. Angelica. Aniseed. Arnica. Asafoetida. Bogbean. Boldo. Buchu. Capsicum. Cassia. Celery. Chamomile (German and Roman). Fenugreek. Horse-chestnut. Horseradish. Liquorice. Meadowsweet. Nettle. Parsley. Passion Flower. Prickly Ash (Northern). Quassia. Wild Carrot. Wild Lettuce

APPENDIX 16 Herbal Ingredients containing Flavonoids

Agnus Castus. Angelica. Aniseed. Apricot. Arnica. Artichoke. Bayberry. Bogbean. Boldo. Boneset. Broom. Buchu. Burdock. Burnet. Calendula. Celery. Cereus. Chamomile (German and Roman). Chaparral. Clivers. Coltsfoot. Cornsilk. Couchgrass. Cowslip. Damiana. Devil's Claw. Drosera. Elder. Eucalyptus. Euphorbia. Eyebright. Fenugreek. Feverfew. Figwort. Frangula. Fumitory. Ginkgo. Gravel Root. Ground Ivy. Hawthorn. Hops. Horehound (Black and White). Horse-chestnut. Hydrangea. Hydrocotyle. Juniper. Lemon Verbena. Lime Flower. Liquorice. Maté. Meadowsweet. Mistletoe. Motherwort. Nettle. Parsley. Passionflower. Plantain. Pulsatilla. Raspberry. Red Clover. Rhubarb. Rosemary. Sarsaparilla. Saw Palmetto. Scullcap. Senna. Shepherd's Purse. Squill. St John's Wort. Thyme. Uva-Ursi. Wild Carrot. Wild Lettuce. Willow. Witch Hazel. Yarrow

APPENDIX 17 Herbal Ingredients containing Iridoids

Agnus Castus. Bogbean. Centaury. Clivers. Devil's Claw. Eyebright. Figwort. Gentian. Ispaghula. Motherwort. Plantain. Scullcap. Uva-Ursi. Valerian. Vervain

APPENDIX 18 Herbal Ingredients containing Saponins

Alfalfa. Aloe Vera. Bogbean. Burnet. Calendula. Chaparral. Cohosh (Blue). Cornsilk. Cowslip. False Unicorn. Fenugreek. Ginseng (Eleutherococcus and Panax). Hawthorn. Horehound (White). Horse-chestnut. Hydrangea. Hydrocotyle. Jamaica Dogwood. Lime Flower. Pokeroot. Pulsatilla. Red Clover. Sarsaparilla. Senega. Senna. Stone Root. Thyme. Yucca

APPENDIX 19 Herbal Ingredients containing Tannins

Agrimony. Apricot. Artichoke. Avens. Bayberry. Blue Flag. Boldo. Borage. Burnet. Calamus. Cascara. Cassia. Chamomile. German. Cinnamon. Clivers. Cohosh (Black). Cola. Coltsfoot. Comfrey. Cornsilk. Cowslip. Damiana. Drosera. Elder. Eucalyptus. Eyebright. Feverfew. Frangula. Gentian. Ground Ivy. Hawthorn. Holy Thistle. Hops. Horse-chestnut. Ispaghula. Juniper. Lady's Slipper. Lime Flower. Marshmallow. Meadowsweet. Mistletoe. Motherwort. Nettle. Pilewort. Plantain. Poplar. Prickly Ash (Northern and Southern). Queen's Delight. Raspberry. Rhubarb. Sage. Sassafras. Saw Palmetto. Scullcap. Slippery Elm. Squill. St John's Wort. Stone Root. Tansy. Thyme. Uva-Ursi. Valerian. Vervain. Willow. Witch Hazel. Yarrow. Yellow Dock

APPENDIX 20 Herbal Ingredients containing Volatile Oils

Agnus Castus. Agrimony. Angelica. Aniseed. Arnica. Artichoke. Asafoetida. Avens. Blue Flag. Boldo. Boneset. Buchu. Burdock. Burnet. Calamus. Calendula. Capsicum. Cassia. Celery. Chamomile (German and Roman). Chaparral. Cinnamon. Cloves. Cohosh (Black). Coltsfoot. Couchgrass. Damiana. Elder. Elecampane. Eucalyptus. Eyebright. Feverfew. Garlic. Ginseng (Eleutherococcus and Panax). Golden Seal. Ground Ivy. Holy Thistle. Hops. Horehound (Black). Horseradish. Hydrocotyle. Juniper. Lemon Verbena. Lime Flower. Liquorice. Lobelia. Meadowsweet. Motherwort. Myrrh. Parsley. Pennyroyal. Prickly Ash (Northern). Queen's Delight. Red Clover. Rosemary. Sage. Sassafras. Saw Palmetto. Senna. Skunk Cabbage. Squill. St John's Wort. Stone Root. Tansy. Thyme. Uva-Ursi. Valerian. Wild Carrot. Witch Hazel. Yarrow