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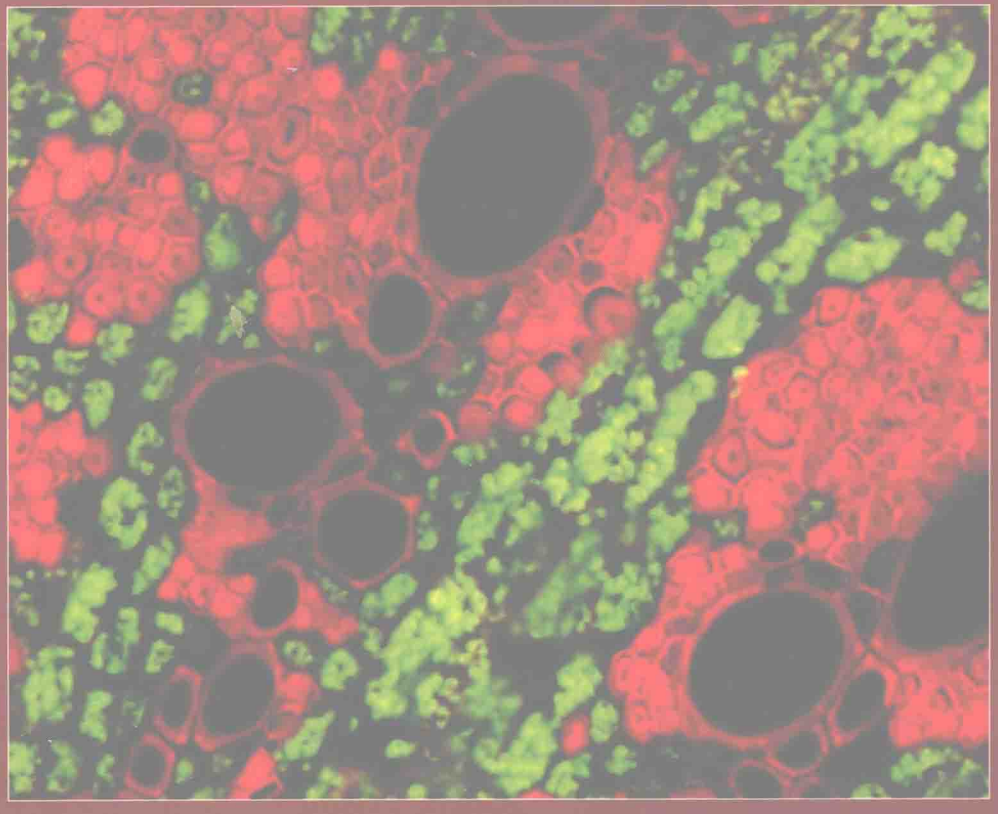

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Meyler's Side Effects of Herbal Medicines

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Meyler's Side Effects of Herbal Medicines

Preface

This volume covers the adverse effects of herbal medicines. The material has been collected from *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions* (15th edition, 2006, in six volumes), which was itself based on previous editions of *Meyler's Side Effects of Drugs*, and from the *Side Effects of Drugs Annuals* (SEDA) 28, 29, and 30. The main contributors of this material were JK Aronson, PAGM de Smet, E Ernst, and M Pittler.

A brief history of the Meyler series

Leopold Meyler was a physician who was treated for tuberculosis after the end of the Nazi occupation of The Netherlands. According to Professor Wim Lammers, writing a tribute in Volume VIII (1975), Meyler got a fever from para-aminosalicylic acid, but elsewhere Graham Dukes has written, based on information from Meyler's widow, that it was deafness from dihydrostreptomycin; perhaps it was both. Meyler discovered that there was no single text to which medical practitioners could look for information about unwanted effects of drug therapy; Louis Lewin's text "Die Nebenwirkungen der Arzneimittel" ("The Untoward Effects of Drugs") of 1881 had long been out of print (SEDA-27, xxv-xxix). Meyler therefore determined to make such information available and persuaded the Netherlands publishing firm of Van Gorcum to publish a book, in Dutch, entirely devoted to descriptions of the adverse effects that drugs could cause. He went on to agree with the Elsevier Publishing Company, as it was then called, to prepare and issue an English translation. The first edition of 192 pages (*Schadelijke Nevenwerkingen van Geneesmiddelen*) appeared in 1951 and the English version (*Side Effects of Drugs*) a year later.

The book was a great success, and a few years later Meyler started to publish what he called surveys of unwanted effects of drugs. Each survey covered a period of two to four years. They were labelled as volumes rather than editions, and after Volume IV had been published Meyler could no longer handle the task alone. For subsequent volumes he recruited collaborators, such as Andrew Herxheimer. In September 1973 Meyler died unexpectedly, and Elsevier invited Graham Dukes to take over the editing of Volume VIII.

Dukes persuaded Elsevier that the published literature was too large to be comfortably encompassed in a four-yearly cycle, and he suggested that the volumes should be produced annually instead. The four-yearly volume could then concentrate on providing a complementary critical encyclopaedic survey of the entire field. The first *Side Effects of Drugs Annual* was published in 1977. The first encyclopaedic edition of *Meyler's Side Effects of Drugs*, which appeared in 1980, was labelled the ninth edition, and since then a new encyclopaedic edition has appeared every four years. The 15th edition was published in 2006, in both hard and electronic versions.

Monograph structure

This volume starts with a general section on the adverse effects of herbal medicines, which is followed by monographs on individual herbal products, each of which has the following structure:

- Family: each monograph is organized under a family of plants (for example Liliaceae).
- Genera: the various genera that are included under the family name are tabulated (for example the family Liliaceae contains 94 genera); the major source of information on families and genera is the Plants National Database (http://plants.usda.gov/index.html).
- Species: in each monograph some species are dealt with separately. For example, in the monograph on Liliaceae, four species are included under their Latin names and major common names—*Sassafras albidum* (sassafras), *Allium sativum* (garlic), *Colchicum autumnale* (autumn crocus), and *Ruscus aculeatus* (butcher's broom).

Each monograph includes the following information in varying amounts:

- Alternative common names; the major sources of this information are *A Modern Herbal* by Mrs M Grieve (1931; http://www.botanical.com/botanical/mgmh/mgmh.html) and *The Desktop Guide to Complementary and Alternative Medicine: an Evidence-Based Approach* by E Ernst, MH Pittler, C Stevenson, and A White (Mosby, 2001).
- Active ingredients; the major source of this information is the *Dictionary of Plants Containing Secondary Metabolites* by John S Glasby (Taylor & Francis, 1991).
- Uses, including traditional and modern uses.
- Adverse effects.
- References.

The families of plants and their species that are the subjects of monographs are listed in Table 2 (p. 14) by alphabetical order of family. The same data are listed in Table 3 (p. 17) by alphabetical order of species. Other monographs cover one of the Basidiomycetes (*Lentinus edodes*, shiitake) and algae. Table 4 (p. 20) gives the Latin equivalents of the common names. To locate a plant by its common name, convert the common name into the Latin name using Table 4 and then find out to which family it belongs by consulting Table 3.

Drug names

Drugs have usually been designated by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available,

chemical names have been used. In some cases brand names have been used.

Spelling

For indexing purposes, American spelling has been used, e.g. anemia, estrogen rather than anaemia, oestrogen.

Cross-references

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-13, SED-14, etc; the *Side Effects of Drugs Annuals* are cited as SEDA-1, SEDA-2, etc.

J K Aronson
Oxford, May 2008

Contents

Herbal Medicines – Introduction and General Information

Herbal Medicines

Introduction

In principle, herbal medicines have the potential to elicit the same types of adverse reactions as synthetic drugs; the body has no way of distinguishing between "natural" and man-made compounds. Herbal medicines consist of whole extracts of plant parts (for example roots, leaves) and contain numerous potentially active molecules. Synergy is normally assumed to play a part in the medicinal effects of plant extracts, and medical herbalists have always claimed that whole plant extracts have superior effects over single isolated constituents. Similarly, it is also claimed that combinations of herbs have synergistic effects. There is in vitro and/or in vivo evidence to support the occurrence of synergism between constituents in certain herbal extracts (1,2); however, clinical evidence is lacking, and it is in any case uncertain how far the principle extends. Synergy is also taken to mean an attenuation of undesirable effects, another key tenet of herbalism being that the toxicity of plant extracts is less than that of a single isolated constituent. However, theoretically, plant constituents could also interact to render a herbal preparation more toxic than a single chemical constituent. Virtually no evidence is available to substantiate either hypothesis. It is also important to determine whether herbal treatments that have been shown to be as effective as conventional drugs have a better safety profile. Contrary to the belief of most herbalists, long-standing experience is by no means a reliable yardstick when it comes to judging the risk of adverse reactions (3).

Uses

Herbal medicine continues to be a growth area. In the UK, retail sales of complementary medicines (licensed herbal medicines, homoeopathic remedies, essential oils used in aromatherapy) were estimated to be £72 million in 1996, an increase of 36% in real terms since 1991 (4). This, however, is likely to be a gross underestimate as popular products sold as food supplements, including *Ginkgo biloba* and garlic, were not included. According to a detailed analysis of the herbal medicines market in Germany and France, total sales of herbal products in those countries in 1997 were US$1.8 billion and US$1.1 billion respectively (5). In 1994, annual retail sales of botanical medicines in the USA were estimated to be around US$1.6 billion; in 1998, the figure was closer to US$4 billion (6).

Some of the most useful data on trends in the use of herbal medicines come from two surveys of US adults carried out in 1991 and 1997/98, which involved over 1500 and over 2000 individuals respectively (7,8). The use of at least one form of complementary therapy in the 12 months preceding the survey increased significantly from 34% in 1990 to 42% in 1997. Herbal medicine was one of the therapies showing the most increase over this time period: there was a statistically significant increase in self-medication with herbal medicine from 2.5% of the sample in 1990 to 13% in 1997 (8). Disclosure rates to physicians of complementary medicine use were below 40% in both surveys (8). Furthermore, 18% of prescription medicine users took prescription medicines concurrently with herbal remedies and/or high-dose vitamins. These aspects of user behaviour clearly have implications for safety.

Several herbal medicines pose serious problems for surgical patients, for example through an increased bleeding tendency (9,10). Vulnerable populations also include children (11), and too few safety data are available to recommend herbal medicines during pregnancy or lactation (12). Several investigators have pointed out the potential of herbal medicines to harm certain organs, for example the liver (13) or the skin (14). Laxatives are often based on herbal extracts, and the risks of herbal laxatives have been emphasized (15). Many authors have reviewed the risks of herbal medicines in general terms (16,17).

The reasons for the popularity of herbal medicine are many and diverse. It appears that complementary medicine is not usually used because of an outright rejection of conventional medicine, but more because users desire to control their own health (5) and because they find complementary medicine to be more congruent with their own values, beliefs, and philosophical orientations toward health and life (18). Also, users may consult different practitioners for different reasons (5). An important reason for the increase in use is that consumers (often motivated by the lay press) consider complementary medicine to be "natural" and assume it is "safe". However, this notion is dangerously misleading; adverse effects have been associated with the use of complementary therapies (19). Furthermore, complementary therapies may not only be directly harmful (for example adverse effects of a herbal formulation), but like other medical treatments have the potential to be indirectly harmful (for example through being applied incompetently, by delaying appropriate effective treatment, or by causing needless expense) (20).

The inadequacy of regulation of herbal medicines has repeatedly been stressed (176). The need for adequate pharmacovigilance of herbal medicine is obvious (177) and guidance for safety assessment has been provided (178).

Adverse effects

Most of the data on adverse effects associated with herbal medicines is anecdotal, and assessment and classification of causality is often not possible. Likewise, there have been few attempts to determine systematically the incidence of adverse effects of non-orthodox therapies.

Several reviews have focused on herbal medicines and have covered:

- the toxicity of medicinal plants (21–23);
- the safety of herbal products in general (24–35; 179–183);
- adverse effects in specific countries, for example the USA (36) and Malaysia (37);
- adverse effects on specific organs (38), such as the cardiovascular system (39; 184), the nervous system (185) the liver (40,41,186–190), the hidneys (191–193) and the skin (42,43);

- the safety of herbal medicines in vulnerable populations: children and adolescents (194–196) elderly patients (44,197), during pregnancy and lactation (45,198–200), patients with cancers (206) and surgical patients (46,47);
- carcinogenicity (48);
- the adverse effects of herbal antidepressants (49);
- the adverse effects of Chinese herbal medicaments (50,51);
- the adverse effects of medicines used in other traditions (52,202–206);
- herb–drug interactions (53–64;207–218);
- pharmacovigilance of herbal medicines (65).

Direct effects associated with herbal medicines can occur in several ways:

- hypersusceptibility reactions
- collateral reactions
- toxic reactions
- drug interactions
- deliberate adulteration and accidental contamination (219)
- false authentication
- lack of quality control.

Some of these effects relate to product quality. While there are some data on certain of these aspects, information on other aspects is almost entirely lacking. For example, there are isolated case reports of interactions between conventional medicines and complementary (usually herbal) remedies (20,66,67), although further information is largely theoretical (68).

Even a perfectly safe remedy (mainstream or unorthodox) can become unsafe when used incompetently. Medical competence can be defined as doing everything in the best interest of the patient according to the best available evidence. There are numerous circumstances, both in orthodox and complementary medicine, when competence is jeopardized:

- missed diagnosis
- misdiagnosis
- disregarding contraindications
- preventing/delaying more effective treatments (for example misinformation about effective therapies; loss of herd immunity through a negative attitude toward immunization)
- clinical deterioration not diagnosed
- adverse reaction not diagnosed
- discontinuation of prescribed drugs
- self-medication.

The attitude of consumers toward herbal medicines can also constitute a risk. When 515 users of herbal remedies were interviewed about their behavior vis a vis adverse effects of herbal versus synthetic over-the-counter drugs, a clear difference emerged. While 26% would consult their doctor for a serious adverse effect of a synthetic medication, only 0.8% would do the same in relation to herbal remedies (69).

The only way to minimize incompetence is by proper education and training, combined with responsible regulatory control. While training and control are self-evident features of mainstream medicine they are often not fully incorporated in complementary medicine. Thus the issue of indirect health risk is particularly pertinent to complementary medicine. Whenever complementary practitioners take full responsibility for a patient, this should be matched with full medical competence; if on the other hand, competence is not demonstrably complete, the practitioner in question should not assume full responsibility (70).

Most reports of adverse effects associated with herbal remedies relate to Chinese herbal medicines (71). This is an issue of growing concern, particularly because in many Western countries the popularity of Chinese herbalism is increasing. This is happening in the almost complete absence of governmental control (72) or of systematic research into the potential hazards of Chinese herbal formulations (73).

There have been several reports of adverse effects associated with Asian herbal formulations (74–94). Most of the serious adverse effects of Chinese herbal remedies are associated with formulations containing aconitine, anticholinergic compounds, aristolochic acid, or podophyllin, contaminating substances (95). Problems with Chinese herbal formulations are intensified because of nomenclature, since common, botanical, and Chinese names exist side by side, making confusion likely.

Frequencies of adverse reactions to herbal medicines

Survey data have repeatedly shown that adverse effects of herbal medicines are more frequent than is generally appreciated. A large US study involving 11 poison centers showed that one-third of the events reported in association with intake of dietary supplements were "greater than mild severity" (220). They included myocardial infarction, liver failure, bleeding, and death. Most frequently implicated were ma huang (*Ephedra*), guaraná, ginseng, and St John's wort. A survey of 2203 Australian therapists suggested that only 17% of these professionals had ever noted an adverse reaction to a herbal treatment (221).

A survey of all patients seen in a German hospital specializing in traditional Chinese medicine included 1036 patients, in 6.5% of whom adverse events (mostly of minor severity) were recorded (222). Several severe adverse events were also noted; they included paralysis of the tibialis anterior muscle, paresthesia, and raised liver enzymes.

A small survey of adverse events after routine practice of Chinese herbal medicine included the data of 144 patients (223). A total of 20 patients reported 32 adverse events associated with Chinese herbal medicines during the 4 weeks after treatment. There were no serious adverse events. The most commonly reported adverse events were diarrhea, fatigue, and nausea.

Of 1701 patients admitted to two general wards of a Hong Kong hospital, 3 (0.2%) had adverse reactions to Chinese herbal drugs; two of the three were serious (96). In a retrospective study of all 2695 patients admitted to a Taiwan department of medicine during 10 months 4% were admitted because of drug-related problems, and herbal remedies ranked third amongst the categories of medicines responsible (97). In an active surveillance adverse drug reaction reporting program conducted in a family medicine ward of the National Taiwan University

Hospital, Chinese crude drugs were responsible for five hospital admissions (22% of the total) or 12% of all adverse reactions observed in the study (98). This is a part of the world where the herbal tradition is particularly strong; the figures do not apply elsewhere.

The incidence of contact sensitization associated with topical formulations containing plant extracts was significant when evaluated in 1032 consecutive or randomly selected patients visiting patch test clinics in The Netherlands (99).

In a 5-year toxicological study of traditional remedies and food supplements carried out by the Medical Toxicology Unit at Guy's and St. Thomas' Hospital, London, 1297 symptomatic enquiries by medical professionals were evaluated (100). Of these, an association was considered to have been confirmed, probable, or possible in 12, 35, and 738 cases respectively. Ten of the confirmed cases were related to Chinese or Indian herbal remedies. As a result of these findings, in October 1996 the UK Committee on Safety of Medicines extended its yellow card scheme for adverse drug reaction reporting to include unlicensed herbal remedies, which are marketed mostly as food supplements in the UK (the scheme had always applied to licensed herbal medicines) (101,102). This was an important milestone in herbal pharmacovigilance.

A report from the Uppsala Monitoring Centre of the WHO has summarized all suspected adverse reactions to herbal medicaments reported from 55 countries worldwide over 20 years (103). A total of 8985 case reports were on record. Most originated from Germany (20%), followed by France (17%), the USA (17%), and the UK (12%). Allergic reactions were the most frequent serious adverse events and there were 21 deaths. The authors pointed out that adverse reactions to herbal medicaments constitute only about 0.5% of all adverse reactions on record.

A hospital-based study from Oman has suggested that 15% of all cases of self-poisoning seen in this setting are with traditional medicines (104). A case series from Thailand has suggested that in patients with oral squamous cell carcinoma the use of herbal medicines before the first consultation with a healthcare professional increases the risk of an advanced stage almost six-fold (105) and survey data from the USA have suggested that herb–drug interactions may be a significant problem in a sizeable proportion of patients (106).

In a German hospital specializing in Chinese herbalism of 145 patients who had been treated within 1 year 53% reported having had at least one adverse effect attributable to Chinese herbal medicines (107). Nausea, vomiting, and diarrhea were the most common complaints. It should be noted that causality in these cases can only be suspected and not proven. In the same institution about 1% of 1507 consecutive patients treated with Chinese herbal mixtures had clinically relevant rises in liver enzymes (108,109). *Glycyrrhiza* radix and *Atractylodis macrocephalae* rhizome were most consistently associated with such problems. In most of these cases there were no associated clinical signs and the abnormalities tended to normalize without specific therapy and in spite of continued treatment with the Chinese herbal mixtures.

When 1100 Australian practitioners of traditional Chinese medicine were asked to complete questionnaires about the adverse effects of Chinese herbal mixtures, they reported 860 adverse events, including 19 deaths (110). It was calculated that each practitioner had encountered an average of 1.4 adverse events during each year of full-time practice.

A physician prospectively monitored all 1265 patients taking traditional Chinese medicines at his clinic during 33 months (111). Liver enzymes were measured before the start of therapy and 3 and 10 weeks later. Alanine transaminase activity was raised in 107 patients (8.5%) who initially had normal values. Of these patients, about 25% reported symptoms such as abdominal discomfort, looseness of bowels, loss of appetite, or fatigue.

A retrospective analysis of all adverse events related to herbal medicines and dietary supplements reported to the California Poison Control System has given data on the risks of the adverse effects of herbal medicines (112). Between January 1997 and June 1998, 918 calls relating to such supplements were received. Exposures resulting in adverse reactions occurred most often at recommended doses. There were 233 adverse events, of which 29% occurred in children. The products most frequently implicated were zinc (38%), *Echinacea* (8%), witch hazel (6%), and chromium picolinate (6%). Most of the adverse events were not severe and required no treatment; hospitalization was required in only three cases.

Table 1 Potential adulterants that should be taken into account in the quality control of herbal medicines

Type of adulterant	*Examples*
Allopathic drugs	Analgesic and anti-inflammatory agents (for example aminophenazone, indometacin, phenylbutazone), benzodiazepines, glucocorticoids, sulfonylureas, thiazide diuretics, thyroid hormones
Botanicals	*Atropa belladonna*, *Digitalis* species, *Colchicum*, *Rauwolfia serpentina*, pyrrolizidine-containing plants (see separate monograph on pyrrolizidines)
Fumigation agents	Ethylene oxide, methyl bromide, phosphine
Heavy metals	Arsenic, cadmium, lead, mercury
Micro-organisms	*Escherichia coli* (certain strains), *Pseudomonas aeruginosa*, *Salmonella*, *Shigella*, *Staphylococcus aureus*
Microbial toxins	Aflatoxins, bacterial endotoxins
Pesticides	Carbamate insecticides and herbicides, chlorinated pesticides (for example aldrin, dieldrin, heptachlor, DDT, DDE, HCB, HCH isomers), dithiocarbamate fungicides, organic phosphates, triazine herbicides
Radionuclides	^{134}Cs, ^{137}Cs, ^{103}Ru, ^{131}I, ^{90}Sr

Adulteration and contamination

Quality control for herbal medicaments that are sold as dietary supplements in most countries is poor (115,116). Concerns about the quality and safety of herbal remedies are justified, and there have been repeated calls for greater control and regulation (75,113,114). Considerable variations in the contents of active ingredients have been reported, with lot-to-lot variations of up to 1000% (117). In most countries, the sale and supply of herbal remedies is to a large extent uncontrolled and unregulated; most herbal remedies are sold as unlicensed food supplements and their safety, efficacy, and quality have therefore not been assessed by licensing authorities. Adulteration and contamination of herbal remedies with other plant material and conventional drugs have been documented (72,118) (Table 1).

The authors of a survey of German importers of Chinese herbs concluded that "only rarely" had herbal drugs to be returned because of contamination (119). The authors also stated that "a 100% check for all possible contaminants is not possible." However, there have been many reports of adulteration and contamination relate to Chinese herbal remedies (120). Instances include adulteration/contamination with conventional drugs (121,122), heavy metals (123–129), and other substances (130,131).

When 27 samples of commercially available camomile formulations were tested in Brazil, it was found that all of them contained adulterants and only 50% had the essential oils needed to produce anti-inflammatory activity (132).

The Botanical Lab in the USA has manufactured the herbal medicines PC-SPES and SPES (133). These two products are marketed as "herbal dietary supplements" for "prostate health" and for "strengthening the immune system" respectively. They are sold through the internet, by mail order, by phone order, and through various distributors and health care professionals. An analytical report from the California Department of Health in 2002 showed that samples of PC-SPES and SPES have been contaminated with alprazolam and warfarin. The Canadian Medicines Regulatory Authority also reported similar contaminations. In view of these reports Health Canada, the Irish Medicines Board, and the State Health Director of California all warned consumers to stop using these two products immediately and to consult their healthcare practitioners. Botanic Lab also informed consumers of these laboratory findings and issued a product recall of all lots of PC-SPES, pending further reports from additional testing of PC-SPES in both commercial and academic laboratories.

In 2002 the Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies, since they contained scheduled medicines and toxic substances (134). The products included the following allopathic drugs:

- Wei Ge Wang tablets, which contained sildenafil
- Sang Ju Gan Mao Pian tablets, which contained diclofenac and chlorphenamine
- Yen Qiao Jie Du Pian capsules, which contained chlorphenamine, diclofenac, and paracetamol
- Xiaoke Wan pills, which contained glibenclamide
- Shuen Feng cream, which contained ketoconazole
- Dezhong Rhinitis drops, which contained ephedrine hydrochloride.

The New Zealand Director General of Health issued a Public Statement asking people to stop taking these products and to seek medical advice. Medsafe asked all importers and distributors of traditional Chinese medicines to cease all distribution and sale of these products, to withdraw them from retail outlets, and to ensure that other products they sell do not contain scheduled medicines.

Benzodiazepines

In 2001 the California State Health Director warned consumers to stop using the herbal product Anso Comfort capsules immediately, because the product contains the undeclared prescription drug chlordiazepoxide. Chlordiazepoxide is a benzodiazepine that is used for anxiety and as a sedative and can be dangerous if not taken under medical supervision (135). Anso Comfort capsules, available by mail or telephone order from the distributor in 60-capsule bottles, were clear with dark green powder inside. The label was yellow with green English printing and a picture of a plant. An investigation by the California Department of Health Services Food and Drug Branch and Food and Drug Laboratory showed that the product contained chlordiazepoxide. The ingredients for the product were imported from China and the capsules were manufactured in California. Advertising for the product claimed that the capsules were useful for the treatment of a wide variety of illnesses, including high blood pressure and high cholesterol, in addition to claims that it was a natural herbal dietary supplement. The advertising also claimed that the product contained only Chinese herbal ingredients and that consumers could reduce or stop their need for prescribed medicines. No clear medical evidence supported any of these claims. The distributor, NuMeridian (formerly known as Top Line Project), voluntarily recalled the product nationwide.

A San Francisco woman with a history of diabetes and high blood pressure was hospitalized in January 2001 with life-threatening hypoglycemia after she consumed Anso Comfort capsules. This may have been due to an interaction of chlordiazepoxide with other unspecified medications that she was taking.

Fenfluramine

There have been reports of herbal remedies adulterated with fenfluramine. Fenfluramine is an appetite suppressant that was banned globally in 1997 because of concerns about its effect on the heart, while nitrosofenfluramine is toxic to the liver.

In 2004 the UK Medicines and Healthcare products Regulatory Agency (MHRA) alerted herbal interest groups and consumers about the presence of fenfluramine and nitrosofenfluramine in an unlicensed traditional Chinese medicine formulation, Shubao Slimming Capsules, supplied illegally as a slimming agent in the UK (224).

There was public health concern in the UK after the referral of a 44-year-old woman with new-onset hypertension, palpitation, anxiety, and a body mass index of 19 kg/m^2. It became apparent that an alarming number of the local population had been attending a particular Chinese herbalist for weight loss remedies. Most had been taking multiple formulations and described "spectacular" results. Several reported considerable cardiovascular symptoms, but they were reassured that Chinese medicines are natural and can cause no harm. Analysis by gas chromatography showed a high concentration of fenfluramine in two of the products (sold as Qian Er and Ma Zin Dol, presumably mimicking the brand name Mazindol). Fenfluramine was also found in the patients' urine. Subsequently, a student nurse was admitted with severe fenfluramine toxicity which developed 2 hours after her first dose of a herbal slimming remedy (136). Following an investigation of this case the Medicines Control Agency published a report on traditional ethnic medicines and the current law (137). Stringent regulation of traditional medicines, at least to the standards of conventional practice, is urgently needed. The hazards associated with the use of dietary supplements containing ma huang, a herbal source of ephedrine, have also been reported (138).

Glucocorticoids

Unregulated Chinese herbal products adulterated with glucocorticoids have been detected (139). Dexamethasone was present in eight of 11 Chinese herbal creams analysed by UK dermatologists. The creams contained dexamethasone in concentrations inappropriate for use on the face or in children (64–1500 micrograms/g). The cream with the highest concentration of dexamethasone was prescribed to treat facial eczema in a 4-month-old baby. In all cases, it had been assumed that the creams did not contain glucocorticoids. The authors were concerned that these patients received both unlabelled and unlicensed topical glucocorticoids. They wrote that "greater regulation and restriction needs to be imposed on herbalists, and continuous monitoring of side effects of these medications is necessary."

When British dermatologists analysed 24 Chinese herbal creams used by their patients for eczema they found that all but four of these samples were adulterated with glucocorticoids (225). Wau Wa cream is marketed in several countries as a herbal cream for eczema. After repeatedly observing surprising therapeutic successes, UK doctors analysed three samples of this cream given to them by three patients (140). The samples contained 0.013% clobetasol propionate, a powerful glucocorticoid that does not occur naturally.

Betamethasone, 0.1–0.3 mg per capsule, has been detected in Cheng Kum and Shen Loon, two herbal medicines that are popular for their benefits in joint pain, skin problems, colds, menopausal symptoms, and dysmenorrhea (141). Over-exposure to betamethasone can result in typical signs of glucocorticoid excess, such as moon face, hypertension, easy bruising, purple abdominal striae, truncal obesity, and hirsutism. The recommended daily adult dose of Cheng Kum is 1–3 capsules per day, and there have been reports of glucocorticoid-induced adverse effects in patients taking Cheng Kum and Shen Loon, even in the absence of other exogenous corticosteroid consumption.

- Two patients, a 29-year-old woman and a 10-year-old girl, developed Cushingoid features after taking Shen Loon for 4 and 5 months respectively (142). Their morning plasma cortisol concentrations were increased and adrenal suppression was confirmed by a short Synacthen test. Both recovered after withdrawal of the remedy and treatment with prednisone.

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has notified that the further importation of these herbal products into New Zealand will be stopped at Customs. However, because of the risk of adrenal suppression from glucocorticoid, consumers have been sent a letter advising them against abruptly discontinuing these products. They should continue with the treatment and see their general practitioner as soon as possible for instructions on how they can be safely weaned off the product. Medsafe has issued a letter to doctors advising them to determine whether patients taking Cheng Kum or Shen Loon are at risk of adrenal suppression by estimating the potential total dose of glucocorticoid (from Cheng Kum or Shen Loon plus any exogenous steroids) and the duration of use, by examining the patient for signs of glucocorticoid excess, and by ascertaining if other risk factors for adrenal suppression are present (such as Addison's disease and AIDS).

The Norwegian Medicines Agency (NoMA) has banned the sale of two herbal medicines, Phu Chee and Lin Chee/Active Rheuma plus, which were found to contain high doses of undeclared dexamethasone (Phu Chee) and prednisolone (Lin Chee/Active Rheuma plus, 226). Physicians from a hospital in northern Norway reported that several patients taking Phu Chee or Lin Chee/Active Rheuma Plus developed symptoms similar to those observed with prolonged use, or high doses, of glucocorticoids, along with subsequent withdrawal symptoms. Laboratory analysis showed that Phu Chee contains dexamethasone 0.4–0.5 mg per tablet and that Lin Chee/Active Rheuma Plus contains an unknown quantity of prednisolone. As the recommended dosage of Phu Chee was 3–9 tablets/day, patients could have been exposed to a daily dose of dexamethasone of 1.2–4.5 mg. NoMA sent a letter to all of the distributors' customers, with a warning about use and rapid discontinuation of the herbal medicines, as well as advice to see a doctor.

Hypoglycemic drugs

Herbal medicines, particularly Chinese ones, are sometimes contaminated with conventional synthetic drugs (143). In 2000 the California Department of Health Services Food and Drug Branch issued a warning to consumers that they should immediately stop using five herbal products because they contained two prescription drugs that were not listed as ingredients and that are

unsafe without monitoring by a physician (144). The products were Diabetes Hypoglucose Capsules, Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Hypoglycemic Capsules, and Zhen Qi Capsules. The products were available by mail order and could be purchased by telephone or via the Internet. Their manufacturers claimed that they contained only natural Chinese herbal ingredients. However, after a diabetic patient in Northern California had had several episodes of hypoglycemia after taking Diabetes Hypoglucose Capsules, an investigation by the Department showed that they contain the antidiabetic drugs glibenclamide (glyburide) and phenformin.

- A 48-year-old diabetic patient from London was initially managed with metformin and gliclazide, but because of poor metabolic control treatment was switched to insulin plus oral metformin (227). His metabolic control remained poor and he developed microvascular and macrovascular complications. He returned to his native India for a visit and on returning his metabolic control was improved. He attributed this to treatment that he had received in India, three different 'herbal balls' to be taken three times a day with meals. The remedies contained chlorpropamide in a dose equivalent to 200 mg/day. It was agreed that the patient should continue with this treatment. One year later, while still taking the 'herbal balls', his metabolic control deteriorated. The herbal therapy was withdrawn and bolus insulin treatment was restarted.

Other compounds

The Chinese patent medicine Hua Fo-Vigor Max is marketed for erectile dysfunction. It was shown by Canadian authorities to contain the prescription drug tadalafil, which is used to treat erectile impotence (228). Health Canada required the importer to remove the product from the market and issued a "Customs Alert" to stop importation of the product.

The regulatory authorities in New Zealand have ordered the withdrawal of 11 Chinese medicines (229). They were adulterated either with *Aristolochia* species, which causes severe kidney damage, or prescription drugs such as sildenafil, diclofenac, chlorphenamine, paracetamol, glibenclamide, ketoconazole, clobetasol, albendazole, and ephedrine. One remedy was contaminated with arsenic.

Jackyakamcho-tang is a Korean herbal mixture of *Paeoniae radix* and *Glycyrrhizae radix*, used for its alleged analgesic and spasmolytic properties. Among 81 patients treated with this remedy there adverse effects in 11%. Indigestion, diarrhea, and edema were the most common complaints; in 3.7% of cases they were rated as severe(230).

The UK Medicines traditional Chinese medicine slimming aid called Qing zhisan tain shou, reportedly contains the prescription-only medicine sibutramine (231). The MHRA has warned consumers that sibutramine should only be prescribed under specific circumstances and requires the supervision of a registered doctor, as it can cause increased blood pressure. Qing zhisan tain shou is supplied in a bicolored cream and a brown capsule formulation. The capsules are contained within blister packs and are presented in a white and green carton with various lettering and imagery. Two other Chinese slimming products, Li da dai dai hua and Meizitang have been seized by the Netherlands' authorities and have been found to contain sibutramine.

Heavy metals

Reports continue to be published on incidents related to the use of traditional herbal medications from China and elsewhere that contain arsenic among other toxic substances (145,146).

There are still occasional cases of patients with late effects from obsolete formulations such as Fowler's solution or neoarsphenamine (SEDA-16, 231). As late as 1998 a case of severe chronic poisoning resulting in fatal multiorgan failure including hepatic portal fibrosis and subsequent angiosarcoma was traced back to exposure to arsenical salts used for the treatment of psoriasis many years before (147) (SEDA-22, 243). In some non-Western countries arsenic is apparently still being used in dentistry for devitalization of inflamed pulp and sensitive dentine, and cases have been described in which this has resulted in arsenical necrosis of the jaws, affecting the maxilla or mandible (148). Some exposure to arsenic may still be occurring from traditional remedies of undeclared composition, and as with other metals there may be environmental contact, notably from semiconductor materials.

In 2002 the Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies, since they contained scheduled medicines and toxic substances (134). The products included Niu Huang Jie Du Pian tablets, which contain 4% arsenic. Of 260 Asian patent medicines available in California, 7% contained undeclared pharmaceuticals. When 251 samples were tested for heavy metals, 24 products contained at least 10 parts per million of lead, 36 contained arsenic, and 35 contained mercury (149).

Cases of adulteration with the heavy metals mercury (150) and lead (151) have been reported.

- A 5-year-old Chinese boy developed motor and vocal tics. His parents had given him a Chinese herbal spray to treat mouth ulcers. The spray contained mercury 878 ppm. Mercury poisoning was confirmed by the blood mercury concentration (183 nmol/l, normal value for adults under 50 nmol/l).
- A 5-year-old boy of Indian origin with encephalopathy, seizures, and developmental delay developed persistent anemia. The more obvious causes were ruled out and his blood lead concentration was high (860 ng/ml). He was treated with chelation therapy and his blood lead concentration fell. For the previous 4 years his parents had given him "Tibetan Herbal Vitamins," produced in

India, which contained large amounts of lead. The investigators calculated that over that time he had ingested around 63 g of lead.

A total of 54 samples of Asian remedies, purchased in Vietnam, Hong Kong, Florida, New York, and New Jersey, were analysed for heavy metal adulteration (152). They contained concentrations of arsenic, lead, and mercury that ranged from merely exceeding published guidelines (74%) to toxic (49%).

Ayurvedic medicines have also been reportedly adulterated and contaminated (153). For example, they have repeatedly been associated with arsenic poisoning, including hyperpigmentation and hyperkeratosis (154). Of 70 unique Ayurvedic products manufactured in India or Pakistan and sold in Boston, mostly for gastrointestinal disorders, 14 contained lead, mercury, and/or arsenic, in concentrations up to about 100 mg/g (155).

In Taipei, 319 children aged 1–7 years were screened for increased blood lead concentrations (156). The consumption of Chinese herbal medicines was significantly correlated with blood lead concentrations. In 2803 subjects from Taipei a history of herbal drug taking proved to be a major risk factor for increased blood lead concentrations (157).

- A 56-year-old woman developed the signs and symptoms of lead poisoning after taking an Indian herbal medicine for many years (158). Her blood and urine lead concentrations were 1530 ng/ml and 4785 μg/day. She also had raised liver enzymes. After withdrawal of the remedy and treatment with penicillamine, she made a full recovery.
- Czech doctors reported the case of a 26-year-old woman who had taken an Ayurvedic remedy (Astrum FE Femikalp) for sterility (159). It contained lead 113 mg/kg. Her blood lead concentration was raised and normalized 1 month after withdrawal of the remedy. Lead poisoning was also confirmed by hair analysis.

There is a practice among urbanized South African blacks to replace traditional herbal ingredients of purgative enemas with sodium or potassium dichromate. This switch can result in serious toxicity, characterized by acute renal insufficiency, gastrointestinal hemorrhage, and hepatocellular dysfunction 160,161.

Toxins

When 62 samples of medicinal plant material and 11 samples of herbal tea were examined in Croatia, fungal contamination was found to be abundant (162). *Aspergillus flavus*, a known producer of aflatoxins was present in 11 and one sample respectively. Mycotoxins were found in seven of the samples analysed.

Micro-organisms

Kombucha "mushroom" is a symbiotic yeast/bacteria aggregate surrounded by a permeable membrane. An outbreak of skin lesions affecting 20 patients from a village near Tehran has been reported (163). The lesions were painless and had a central black necrotic area, marginal erythema, and severe peripheral edema. These clinical signs led to the suspicion of anthrax infection. It turned out that all patients had applied Kombucha mushroom locally as a painkiller. The skin lesions had developed 5–7 days after the application of the material. Cultures from the skin lesions confirmed the presence of *Bacillus anthracis*. Cultures of the Kombucha mushrooms were inconclusive, owing to multiple bacterial contamination and overgrowth, but it was shown that anthrax would grow on uncontaminated material. The patients all recovered with antibiotic therapy.

Pesticides

Some herbal medicaments are contaminated with pesticides (164).

Herbal mixtures containing various ingredients: Organs and systems

Numerous herbal mixtures are promoted worldwide, for example through the Internet. In many cases their herbal ingredients are not disclosed.

Cardiovascular

Severe hypotension has been attributed to a Chinese herbal mixture (232).

- A 57-year-old man developed nausea, epigastric pain, dizziness, and diarrhea 4 hours after taking a decoction made of 14 Chinese herbs. On admission his blood pressure was 77/46 and his pulse 6 per minute. He was given intravenous fluids and the hypotension normalized within hours.

The authors pointed out that seven of the 14 herbal constituents are known to have vasodilatory effects. They therefore believed that this herbal mixture synergistically caused the hypotensive crisis.

Respiratory

Sho-saiko-to is a so-called kampo medicine, a mixture of herbs, including Chinese date, ginger root, and licorice root. It is reportedly contraindicated in patients taking interferons, patients with liver cirrhosis or hepatoma, and patients with chronic hepatitis and a platelet count of 100×10^9/l (http://www.kamponews.com). Sho-saiko-to has repeatedly been implicated in interstitial or eosinophilic pneumonias.

- A 45-year-old woman developed a high fever, a nonproductive cough, and severe dyspnea (171). Her chest X-ray showed bilateral alveolar infiltrates. Treatment with antibiotics was not successful and her condition deteriorated. She was finally put on mechanical ventilation and subsequently improved dramatically. It turned out that she had previously taken sho-saiko-to for liver dysfunction of unknown cause.

Based on a positive lymphocyte stimulation test, the authors were confident that this herbal remedy had caused pulmonary edema.

Nervous system

Cholinergic poisoning has been attributed to a Chinese herbal mixture, Ting kung teng.

- A 73-year-old man developed a cholinergic syndrome, with dizziness, sweating, chills, lacrimation, salivation, rhinorrhea, nausea, and vomiting after taking the Chinese patent medicine Ting kung teng for arthritis (174). The herbal mixture contained tropane alkaloids with cholinergic activity. After withdrawal of the remedy he made a swift and complete recovery.

Sensory systems

Corneal opacities causing photophobia have been attributed to a Kampo medicine (172).

- A 30-year-old Japanese woman developed bilateral photophobia. There were dust-like opacities in both corneae. She had a superficial keratectomy, and electron microscopy identified the opacities as lipid-like particles. She had intermittently taken a Kampo medicine composed of 18 different herbal ingredients. Her photophobia coincided with episodes of taking this medicine. The remedy was withdrawn and her symptoms subsequently subsided. She then abstained from the Kampo medicine without recurrence.

Psychiatric

Herbalife is a complex herbal formula that is promoted for weight loss. Acute mania has been attributed to it (168).

- A 39-year-old man developed classic symptoms of mania within 4–72 hours of taking Herbalife. He continued to take it and after several days became psychotic, paranoid, and out of control, culminating in a high-speed car chase with the police. Bipolar disorder was diagnosed and treated, including withdrawal of the Herbalife, and he remained free of symptoms 3 months later.

The author thought it likely that the herbal mixture had caused the psychotic illness in a man who had no previous history of mental disturbance.

Liver

Japanese authors have reported 12 cases of acute liver damage associated with Chaso or Onshido, two Chinese herbal aids to weight loss (233). Both supposedly herbal medicines actually contained N-nitroso-fenfluramine. Most patients made a full recovery, but one died and one required liver transplantation. A health warning about these medicines was issued in Japan, and subsequently 474 further cases of hepatotoxicity induced by herbal aids to weight loss came to light. The nature of the liver injury and its exact cause is not entirely clear. The pathology was consistent with toxic hepatitis.

- A 31-year-old woman developed severe hepatotoxicity while taking the Chinese drug Onshidou- Genbi-Kounou for weight loss (234). Her condition improved after withdrawal of the remedy. Other possible causes were excluded.

The authors believed that the Chinese medicine had caused the hepatitis.

- A 52-year-old woman developed liver damage resembling chronic hepatitis while taking the herbal weight loss aid "Be Petite" (235). After withdrawal of the product her signs and symptoms improved, and at 4 months follow-up she had recovered fully.

In the absence of other risk factors, the authors believed that "Be Petite" may have caused this hepatotoxic event.

- When a 37-year-old woman was admitted for elective surgery her liver enzymes and prothrombin time were found to be abnormal (236). The most plausible reason for this was that she was taking Chinese herbal mixtures containing a total of 61 different herbal ingredients. She was operated on after withdrawal of the herbal medicines for 4 days and developed a vaginal vault hematoma postoperatively. She was discharged free of symptoms on day 17.
- A 37-year-old woman developed toxic hepatitis and a vaginal vault hematoma after hysterectomy (237). She had been taking a Chinese herbal mixture containing 61 different ingredients for 6 weeks. Her prothrombin time and liver enzymes were abnormal. No other reason for her medical problems was identified. Her herbal prescription included ingredients known to have hepatotoxic and anticoagulant properties. The remedy was withdrawn and she made an uneventful recovery.

Copaltra is a herbal tea sold in France as an adjuvant therapy for diabetes. It contains *Coutarea latiflora* (50 g) and *Centaurium erythreae* (50 g).

- A 49-year-old black woman was admitted with jaundice and raised liver enzymes 4 months after starting to take Copaltra (166). She also took fenofibrate, polyunsaturated fatty acids, metformin, benfluorex, and veralipride. Liver biopsy confirmed the diagnosis of acute, severe, cytolytic hepatitis, most likely drug-induced. She made a full recovery after withdrawal of Copaltra.

The authors mentioned that five similar cases of Copaltra-induced hepatitis have been reported to the French authorities.

Isabgol is an Italian herbal mixture that is promoted for constipation.

- Syncytial giant cell hepatitis occurred in a 26-year-old woman who used Isabgol (169). Autoimmune disease and viral infections were excluded.

The authors felt that the causative role of the Isabgol was supported by the spontaneous and dramatic clinical, biochemical, and histological improvement that followed the withdrawal of Isabgol without any further therapy.