SAFETY OF HERBAL MEDICINAL PRODUCTS

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A. INTRODUCTION

A.1 This report provides an overview of the safety issues associated with herbal medicinal products. It has been compiled by Medicines Control Agency (MCA) in response to a request from Members of Parliament and herbal interest groups for background information to inform discussions on the proposed Directive on Traditional Herbal Medicinal Products.

A.2 In general, most herbal medicinal products are unlikely to pose a significant threat to human health, nonetheless, the following report highlights issues that have arisen which have given rise to public health concerns.

B. REGULATION OF HERBAL MEDICINAL PRODUCTS

B.1 The MCA's primary objective is to protect public health by ensuring that all medicines, including unlicensed products, are safe and of suitable quality.

B.2 To obtain a marketing authorisation (product licence) within the EU, applicants for herbal medicinal products are required to demonstrate that their products meet acceptable standards of quality, safety and efficacy. In the UK there are alternative regulatory routes for herbal medicinal products.

- **Licensed herbal medicines:** to receive a marketing authorisation, herbal medicines are required to meet safety, quality and efficacy criteria in a similar manner to any other licensed medicine. The product must be appropriately labelled and be supplied with a Patient Information Leaflet setting out how to use the medicine and detailing possible contra-indications, warnings and potential interactions with other medicines.

- **Herbal remedies exempt from licensing requirements:** the exemption applies where herbal remedies meet conditions set out in Section 12 of the Medicines Act 1968. Certain toxic plants are not permitted (see below: ***Existing Restrictions on Toxic Plant Species***). Apart from these restrictions, there are no specific

safeguards on quality and safety for unlicensed herbal remedies. Furthermore, in contrast to licensed products, with unlicensed herbal remedies, there are no statutory provisions for labelling or information to be provided to the patient.

B.3 The MCA has reached a wide measure of agreement with the UK herbal sector that the current arrangements for unlicensed herbal medicinal products do not afford sufficient protection for public health and that there is a need to improve the regulatory position.

Existing Restrictions on Toxic Plant Species

B.4 In the UK, certain potent and potentially hazardous plant species are restricted to use by medical practitioners by the Prescription Only Medicines (Products Other than Veterinary Drugs) Order 1997. These include for example, *Digitalis,* Nux Vomica (*Strychnos)*, Aconite, Croton Seed, *Rauwolfia*.

B.5 Certain other potentially hazardous herbal ingredients are controlled under The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977. This Order (Part I) specifies 25 plants which cannot be supplied except via a pharmacy, and includes toxic species such as *Areca, Crotalaria, Dryopteris and Strophanthus*. In Part II, the Order specifies plant species such as *Aconitum, Atropa, Ephedra and Hyoscyamus*, which can be supplied following one-to-one consultation by permitted routes of administration at specified doses (**Appendix 1**).

B.6 Legislation (The Medicines (Aristolochia and Mu Tong etc) (Prohibition) Order 2001) prohibits in unlicensed medicine *Aristolochia* species and a number of other herbal ingredients which can be confused with *Aristolochia.* These measures were introduced following reports of serious cases of renal toxicity and evidence of substitution of certain ingredients in traditional Chinese medicines (TCM).

Review of restricted herbal ingredients

B.7 MCA has recently considered the need to update the list of herbal ingredients subject to restrictions or prohibitions in use in unlicensed medicines. The primary focus is on ingredients used in ethnic medicines. This reflects the position that at the time of the last systematic review which led to the 1977 list of restricted ingredients, use of TCM and Ayurvedic medicines in the UK was much less prevalent than is now the case.

B.8 Informal consultation has commenced on a number of herbal ingredients where the MCA has provisional concerns on public health grounds (**Appendix 2).**

C. SAFETY OF HERBAL MEDICINAL PRODUCTS

C.1 The safety concerns arising with herbal medicinal products are summarised below; a more detailed overview follows.

C.2 The use of traditional medicines (TM) and complementary and alternative medicine (CAM), in particular the use of herbal medicinal products, continues to grow world-wide. In their recent report (*WHO Traditional Medicine Strategy 2002-2005*) WHO have highlighted that [(1)]:

> *'The use of TM/CAM is increasing rapidly in developed countries. In many parts of the world, policy-makers, health professionals and the public are wrestling with questions about the safety, quality, availability, preservation and further development of this type of health care.*
>
> *Although many TM/CAM therapies have promising potential, and are increasingly used, many of them are untested and their use not monitored. As a result, knowledge of their potential side-effects is limited. This makes identification of the safest and most effective therapies, and promotion of their rational use more difficult. If TM/CAM is to be promoted as a source of healthcare, efforts must be made to promote its rational use, and identification of the safest and most effective therapies will be crucial.'*

C.3 Over the past decade important safety issues associated with the use of herbal products have resulted in regulatory action world-wide in an effort to protect public health. The substitution of toxic *Aristolochia* species in traditional Chinese medicines (TCM) has resulted in cases of serious renal toxicity and renal cancer in Europe, China and America.

C.4 The safety problems emerging with herbal medicinal products reflect a growing market, largely unregulated, where many of the safety concerns arise due to lack of effective quality controls. No such parallel exists with regulated medicinal products.

C.5 Concerns about the poor quality and safety standards of traditional Chinese medicines in particular, were expressed in September 2001. The MCA was continuing to find examples of TCMs containing potentially dangerous and often illegal ingredients that posed a risk to public health. The MCA held a press conference to alert the public via the media of the advice of Committee on Safety of Medicines (CSM) that it was unable to give the public any general assurances as to the safety of TCMs on the market (**Appendix 3).**

C.6 Other serious quality related safety problems include the deliberate addition of prescription medicines and toxic heavy metals to herbal products. Recent examples in the UK include the presence of:

- corticosteroids in creams intended for use in children with eczema
- fenfluramine in a slimming product

- other prescription medicines (sildenafil, glibenclamide, warfarin, alprazolam) in herbal products.

C.7 Increased usage and possibly increased awareness of potential safety concerns have identified hitherto unknown safety problems with some traditional herbal products. Serious liver toxicity (including 3 fatal cases and 6 cases resulting in liver transplants) associated with the use of Kava-kava (*Piper methysticum*) has been reported recently. In July 2002 the CSM advised that the use of Kava-kava should be prohibited in unlicensed medicinal products and in the light of this advice, the MCA has launched a public consultation (**Appendix 4**).

C.8 Other concerns, particularly interactions with conventional medicines, are the consequence of using conventional medicines and herbal products simultaneously and are no surprise from a scientific viewpoint. Interactions, particularly those with medicines, can and do give rise to serious public health concerns.

C.9 The potential for herb-drug interactions has been highlighted by recognition that the widely used herbal remedy, St John's Wort (*Hypericum perforatum*), may interact with certain important medicines. These include for example HIV protease inhibitors, oral contraceptives, cyclosporin and warfarin, leading to a loss or reduction in the therapeutic effect of these prescribed medicines.

C.10 The risks to HIV patients of ineffective therapy are obvious; with ciclosporin, ineffective therapy has resulted in cases of patients rejecting newly transplanted organs (heart and kidney transplants) and pregnancies resulting from interactions with oral contraceptives have been reported, including 7 cases in the UK. UK cases are summarised in **Table 1**.

Table 1.
Reports of suspected interactions between St John's Wort and conventional medicines received by the UK Committee on Safety of Medicines for the period October 1996 to June 2002

Compound or medicine	Reports	Comment
Warfarin	4	Increased INR (2 reports); decreased INR (2 reports)
SSRIs	4	Paroxetine (3 reports); Sertraline (1 report)
Theophylline	1	Reduced serum theophylline concentration
Indinavir, lamivudine, stavudine	1	HIV viral load increased
Tacrolimus	1	Medicine ineffective
Oral contraceptives	14	Intermenstrual bleeding (6 reports); unintended pregnancy (8 reports)
Others	15	Including: HRT (2 reports), atorvastatin (1 report), moclobemide (1 report), verapamil (1 report), enalapril (1 report), lithium (1 report), thyroxine (1 report)

† Source: Medicines Control Agency Adverse Drug Reactions Online Information Tracking (ADROIT)
INR = international normalised ratio; SSRIs = selective serotonin reuptake inhibitors

Protecting public health

C.11 The MCA's primary objective is to protect public health by ensuring that all medicines, including unlicensed products, are safe and of suitable quality. To help achieve this, the MCA has tried to ensure that consumers, companies and health care professionals are informed about herbal medicines that may pose a risk to human health.

C.12 There is, however, a widespread perception amongst the public that herbal medicines being 'natural' are entirely 'safe'. The fact is that many plants are well known to present a direct hazard to human health (Foxglove (*Digitalis*), Deadly Nightshade (*Belladonna*), *Aristolochia* and are thus subject to strict controls. Other plants can be unsafe if used for example, during pregnancy eg. Pennyroyal.

C.13 There is a need for the public to have an understanding of the risks posed by herbal medicines to ensure that such products are used safely. As highlighted above, the safety of some unlicensed herbal products is compromised by lack of suitable quality controls, inadequate labelling and the absence of appropriate patient information.

C.14 In an effort to improve information to the public, MCA has recently launched a specialist area of the web-site entitled, *Herbal Safety News*, to bring together current issues related to herbal product safety (**Appendix 5**). It is hoped that the information on the web-site will help widen awareness of the safety issues raised by the use of herbal medicines and in doing so, help to protect public health.

C.15 As regards informing health care professionals, the MCA publishes current issues relating to the safety of herbal medicines in the MCA bulletin "Current Problems in Pharmacovigilance". This information is distributed to all health professionals in the UK.

Reporting of Adverse Reactions to Herbal Medicinal Products

C.16 It is essential that information on the risks associated with the use of herbal products is systematically collected and analysed in order to protect public health. In 1996, the UK the MCA extended its 'Yellow Card Scheme' to include reporting of suspected adverse reactions to unlicensed herbal products. This followed a report from Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal remedies. Twenty-one cases of liver toxicity, including two deaths, were associated with the use of TCM.

C.17 MCA issues frequent reminders to health professionals to report any suspected adverse reaction to any herbal remedies via the MCA Bulletin "Current Problems in Pharmacovigilance" and the web-site information.

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OVERVIEW OF SAFETY PROBLEMS ARISING WITH HERBAL MEDICINAL PRODUCTS

1. INTRODUCTION

1.1 As with all forms of self-treatment, the use of herbal medicinal products presents a potential risk to human health. [2] The safety concerns fall into 5 main categories:

- Self-administration of any therapy in preference to conventional treatment may delay a patient seeking qualified advice, or cause a patient to abandon conventional treatment without first seeking appropriate advice.

- The patient may be exposed to potentially toxic substances present naturally in the herbal ingredients (ie. intrinsically toxic constituents).

- The patient may be at risk of toxicity as a result of exposure to contaminants present in the herbal product (ie. quality related safety issues).

- Herbal medicinal products may in some cases compromise the efficacy of conventional medicines, for example through herb-drug interactions.

- Specific patient groups may be at risk eg. pregnant or nursing mothers, children, the elderly.

2. SELF-MEDICATION

2.1 The safety of herbal medicinal products is of particular importance as the majority of these products are self-prescribed and are used to treat minor and often chronic conditions. Recent research highlights the fact that patients are reluctant to tell their doctors that they are taking herbal products and thus it is probable that adverse reactions to herbal products are under-reported. [3]

2.2 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. [2, 4] 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 toxicity that are of most concern when assessing the safety of herbal remedies.

2.3 The results of a survey carried out by the UK National Poisons Unit from 1991 to 1995 on potentially serious adverse reactions associated with exposure to traditional medicines and food supplements have been published. [5] Of 1297 inquiries, 785 cases were identified as possible or definitive cases of poisoning caused by traditional medicines or food supplements. The report concluded that the overall risk to public health was low, however, clusters of cases were identified that gave cause for concern. Twenty-one cases of liver toxicity, including two deaths were associated with the use of traditional Chinese medicines although no causative agent was identified.

3. INTRINSICALLY TOXIC CONSTITUENTS OF HERBAL INGREDIENTS

3.1 Limited toxicological data are available on medicinal plants. However, there exists a considerable overlap between those herbs used for medicinal purposes and those used for cosmetic or culinary purposes, for which a significant body of information exists. For many culinary herbs used in herbal remedies, there is no reason to doubt their safety providing the intended dose and route of administration is in line with their food use. When intended for use in larger therapeutic doses the safety of culinary herbs requires re-evaluation.

3.2 Culinary Herbs

Some culinary herbs contain potentially toxic constituents. The safe use of these herbs is ensured by limiting the level of constituent permitted in a food product to a level not considered to represent a health hazard.

- *Apiole* The irritant principle present in the volatile oil of parsley is held to be responsible for the abortifacient action. [6] Apiole is also hepatotoxic and liver damage has been documented as a result of excessive ingestion of parsley, far exceeding normal dietary consumption, over a prolonged period. [6]

- β-*Asarone* Calamus rhizome oil contains β-asarone as the major component, which has been shown to be carcinogenic in animal studies. [6] Many other culinary herbs contain low levels of β-asarone in their volatile oils and therefore the level of β-asarone permitted in foods as a flavouring is restricted.

- *Estragole (Methylchavicol)*Estragole is a constituent of many culinary herbs but is a major component of the oils of tarragon, fennel, sweet basil, and chervil. Estragole has been reported to be carcinogenic in animals. [6] The level of estragole permitted in food products as a flavouring is restricted.

- *Safrole* Animal studies involving safrole, the major component of sassafras oil, have shown it to be hepatotoxic and carcinogenic. [6] The permitted level of safrole as a flavouring in foods is 0.1 mg/kg.

3.3 Other Intrinsically Toxic Constituents

- *Aristolochic Acids*
  These are reported to occur only in the *Aristolochiaceae* family. They have been reported in *Aristolochia* species and appear to occur throughout the plant in the roots, stem, herb and fruit. The aristolochic acids are a series of substituted nitrophenanthrene carboxylic acids. The main constituents are 3,4-methylenedioxy-8-methoxy-10-nitrophenanthrene-1-carboxylic acid. Low levels of aristolochic acids have been reported in Asarum species, another member of the *Aristolochiaceae* family. Aristolochica acids have been shown to be nephrotoxic, carcinogenic and mutagenic. [7]

- *Pyrrolizidine Alkaloids* (PAs)
  These are present in a number of plant species, notably *Crotalaria, Heliotropium and Senecio*. Many of these plants have been used in African, Caribbean and South American countries as food sources and as medicinal 'bush teas'. These alkaloids are known to injure the liver in humans giving rise to serious liver damage (hepatic veno-occlusive disease). This hepatotoxicity associated with their consumption is well documented and has been attributed to the pyrrolizidine alkaloid constituents. [8,9] Pyrrolizidine alkaloids can be divided into two categories based on their structure, namely those with an unsaturated nucleus (toxic) and those with a saturated nucleus (considered non- toxic). A number of herbs currently used in herbal remedies contain pyrrolizidines; they include liferoot (*Senecio aureus*), borage and comfrey.

  In addition to various animal studies, two cases of human hepatotoxicity associated with the ingestion of comfrey have been documented. [10,11] Following advice of the Committee on Review of Medicines (CRM) comfrey has been removed from all licensed products intended for internal use. It is permitted as an ingredient of products intended for external use on unbroken skin.

  It has come to the attention of MCA that a traditional Chinese medicine (TCM) product known by the name of Qianbai Biyan Pian has been supplied in the UK. This herbal product contains *Senecio scandens* which is known to contain the unsaturated pyrrolizidine alkaloids, senecionine and seneciphylline. MCA has advised patients to discontinue use of the product and to consult their doctor. Manufacturers have been advised to cease supply of products containing this ingredient. The concerns about the potential toxicity of *Senecio scandens* have been highlighted on the MCA web-site (**Appendix 5**).

- *Benzophenanthridine Alkaloids*
  These are present in bloodroot and in prickly ash. Although some of these alkaloids have exhibited cytotoxic properties in animal studies, their toxicity to humans has been refuted.

- *Lectins*
  These are plant proteins which possess haemagglutinating and potent mitogenic properties. Both mistletoe and pokeroot contain lectins. Systemic exposure to pokeroot has resulted in haematological aberrations. Mistletoe lectins may also inhibit protein synthesis.[12]

- *Viscotoxins*
  These are constituents of mistletoe, are low molecular weight proteins which possess cytotoxic and cardiotoxic properties.[12] For many years, mistletoe preparations have been used in Europe as cancer treatments. Clinical trials carried out with Iscador™, a product produced from the naturally fermented plant juice of mistletoe, have concluded that Iscador™ may exhibit some weak antitumour effects but should only be used alongside conventional therapy in the long term treatment of cancer.

- *Lignans*
  Hepatotoxic reactions reported for chaparral have been associated with the lignan constituents.

- *Saponins*
  Pokeroot also contains irritant saponins which have produced severe gastrointestinal irritation involving intense abdominal cramping and haematemesis. Systemic exposure to these saponins has resulted in hypotension and tachycardia. In May 1979, the US Herb Trade Association requested that all its members should stop selling pokeroot as a herbal beverage or food because of its toxicity. [13]

- *Diterpenes*
  The irritant properties of many diterpenes are well documented and queen's delight contains diterpene esters which are extremely irritant to all mucosal surfaces .

- *Cyanogenetic Glycosides*
  Cyanogenetic glycosides are present in the kernels of a number of fruits including apricot, bitter almond, cherry, pear, and plum seeds. Gastric hydrolysis of these compounds following oral ingestion results in the release of hydrogen cyanide (HCN), which is rapidly absorbed from the upper gastrointestinal tract and which can lead to respiratory failure. It has been estimated that oral doses of 50 mg of HCN can be fatal, equivalent to about 50-60 apricot kernels [14] However, variation in cyanogenetic glycoside content of the kernels could reduce or increase the number required for a fatal reaction. In the early 1980s a substance called amygdalin was promoted as a ‘natural’ non-toxic cure for cancer. Amygdalin is a cyanogenetic glycoside that is also referred to as laetrile and vitamin B_{17}. Two near-fatal episodes of HCN poisoning were recorded in which the patients had consumed apricot kernels as an alternative source of amygdalin, due to the poor availability of laetrile. Scientific research did not support the claims made for laetrile, although a small number of anecdotal reports suggested that laetrile may have some slight anticancer activity.

As a result, UK legislation drawn up in 1984 [15] restricts the availability of cyanogenetic substances so that amygdalin can only be administered under medical supervision.

- *Furanocoumarins*
  These are found predominantly in the orders Umbelliferae (Parsley, Celery), Rutaceae (eg. Bergamot, Citrus species), Moraceae and Leguminosae. The furanocoumarins occur as linear and branched forms: the most commonly reported linear furanocoumarins are 8-methoxypsoralen, 5-methoxypsoralen (bergapten) and psoralen itself. The furanocoumarins are phototoxic.

  Severe phototoxic reactions have been reported in humans following the use of Bergamot oil in topical preparations. Severe phototoxic burns have been reported in a Swedish patient following a visit to a suntan parlour after ingestion of a large quantity of celery soup. [16]

  In the UK, a patient developed severe phototoxicity during oral photochemotherapy with psoralen and ultraviolet A (PUVA) after eating a large quantity of soup made from celery, parsley and parsnip. [17] The authors highlighted the potential hazards of eating foods containing psoralens during PUVA therapy.

  More recently in the UK, two reports of severe skin burns were received by the MCA where the patients were treated with uncontrolled TCM preparations derived from *Psoralea corylifolia* fruit. [18]

3.4 Herbal Ingredients that may cause Adverse Effects

Examples of adverse effects that have been documented in humans or animals for the herbal ingredients described in the monographs are summarised in **Table 2.** These adverse effects include allergic, cardiac, hepatic, hormonal, irritant, and purgative effects, and a range of toxicities.

The following examples are illustrative of some of the adverse effects caused by herbal ingredients.

- *Comfrey, Coltsfoot*
  Hepatotoxic reactions have been documented for comfrey and coltsfoot. Both of these herbal ingredients contain pyrrolizidine alkaloids, compounds known to be hepatotoxic. However, it was later reported that the reaction documented for coltsfoot may have in fact involved a herbal tea containing a *Senecio* species rather than coltsfoot. [19] The *Senecio* genus is characterized by its pyrrolizidine alkaloid constituents.

- *Mistletoe, Scullcap*
  A case of hepatitis has been reported for a woman who was taking a multi-constituent herbal product. Based on the known toxic constituents of mistletoe and other herbal ingredients present in the product, it was concluded that mistletoe was the component responsible for the hepatitis. Lectins and viscotoxins, the toxic constituents in mistletoe, are not known to be hepatotoxic and no other reports of

liver damage associated with mistletoe ingestion have been documented. The product also contained scullcap, which is recognised to be frequently adulterated with a *Teucrium* species. Recently, hepatotoxic reactions have been associated with germander (*Teucrium chamaedrys*).

- *Pokeroot*
  Severe gastrointestinal irritation and haematological abnormalities documented for pokeroot can be directly related to the saponin and lectin constituents of pokeroot. [19]

- *Sassafras*
  Hepatotoxicity has been associated with the consumption of a herbal tea containing sassafras. The principal component of sassafras volatile oil is safrole, which is known to be hepatotoxic and carcinogenic. [6]

3.5 Excessive Ingestion

- *Ginseng*
  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. However, side-effects have also been reported for ginseng following the ingestion of recommended doses, and include mastalgia and vaginal bleeding. [20]

- *Liquorice*
  Excessive ingestion of liquorice has resulted in typical corticosteroid-type side-effects of oedema and hypertension. [21]

- *Parsley*
  Parsley volatile oil contains apiole which is structurally related to the recognised hepatocarcinogen, safrole. Ingestion of apiole has resulted in a number of cases of fatal poisoning. [6]

3.6 Hypersensitivity Reactions

- *Chamomile*
  Sesquiterpene lactones are known to possess allergenic properties. They occur predominantly in herbs of the Compositae (Asteraceae) family, of which chamomile is a member. Hypersensitivity reactions have been reported for chamomile and other plants from the same family. Cross-sensitivity to other members of the Compositae family is well recognised.

- *Feverfew*
  The sesquiterpene lactones present in feverfew are considered to be the active principles in the herb. It is unknown whether documented side-effects for feverfew, such as mouth ulcers and swollen tongue, are also attributable to these constituents. [22]

3.7 **Phototoxic Reactions**

- *Parsley*
  Furanocoumarins, compounds known to cause phototoxic reactions, are constituents of parsley. Excessive ingestion of parsley has been associated with the development of photosensitive rash which resolved once parsley consumption ceased. [6]

4. QUALITY RELATED SAFETY ISSUES

Over the past decade the quality of herbal products has continued to be a significant concern with regard to the safety of herbal products. The importance of quality in ensuring the safety and efficacy of herbal products has been reviewed extensively. [19, 23-26]

4.1 **Problems with unregulated herbal products**

The great majority of quality related problems are associated with unregulated herbal products. There is substantial international evidence that quality controls in relation to some ethnic medicines, in particular, those used in Traditional Chinese Medicine (TCM) and traditional Asian medicines (Ayurvedic and Unani), may be variable and may give rise to public health concerns. The problems include:

- deliberate or accidental inclusion of prohibited or restricted ingredients
- substitution of ingredients
- contamination with toxic substances
- differences between the labelled and actual contents.

These problems are further compounded by demand outstripping supply of good quality ingredients, confusing nomenclature over plant species, cultural differences of view over toxicity and traditional practices such as substituting one ingredient for another having a reportedly similar action.

The MCA has established an ethnic medicines forum to encourage and assist the UK ethnic medicines sector to achieve improvements to safety and quality standards in relation to unlicensed ethnic medicines. This is in advance of any improvements to the regulatory regime that might emerge from current policy initiatives within the EU on the traditional use directive **(Appendix 1).**

4.1.1 **Substitution and adulteration**

- ***Aristolochia***

  In what must be the most significant cause of plant toxicity in the last decade, inadvertent exposure to *Aristolochia* species in unlicensed herbal medicines has resulted in cases of nephrotoxicity and carcinogenicity in Europe, China, Japan and USA. Concerns were first raised about the effects of products containing aristolochic acids in Belgium where since 1993 over 100 cases of irreversible nephropathy have been reported in young women attending a slimming clinic. The nephrotoxicity was traced to the inadvertent use of the toxic *Aristolochia fangchi* root in the formulations as a substitute for *Stephania tetrandra*. Aristolochic acids, the toxic components of *Aristolochia* species are known to be nephrotoxic, carcinogenic and mutagenic. A number of the Belgian patients have subsequently developed urothelial cancer as a result of exposure to the toxic aristolochic acids.[27-30]

  Seven cases of nephropathy involving substitution of *Aristolochia fangchi* and *Stephania tetrandra* have been reported in France.[31]

  Other cases of toxicity have involved the substitution of *Aristolochia manshuriensis* stem for the stem of *Clematis* and *Akebia* species.[31] In the UK, two such cases of end stage renal failure were reported in 1999.[32]

  Other cases have been reported in China (seventeen cases with twelve fatalities) and Japan (ten cases of renal failure).[31] Recently, the FDA have reported two cases of serious renal disease due to *Aristolochia* being substituted for *Clematis* species in a dietary supplement.[33]

  Substitution of one plant species for another, often of a completely different genus, is an established practice in TCM. Furthermore, herbal ingredients are traded using their common Chinese Pin Yin names and this can lead to confusion. For example, the name Fangji can be used to describe the roots of *Aristolochia fangchi, Stephania tetrandra or Cocculus* species and the name Mu Tong can be used to describe the stem of *Aristolochia manshuriensis, Clematis* or *Akebia* species.

  The widespread substitution with *Aristolochia* species in TCM products available in the UK has been confirmed in a recent MCA study which reported the presence of aristolochic acids in 44%(28) of TCM products containing Fang ji and Mu Tong. [34]

  The problems associated with *Aristolochia* have prompted regulatory action world-wide and new legislation has been introduced in the UK to prohibit the use of *Aristolochia* species in unlicensed medicines in the UK. The EMEA has produced a position paper on *Aristolochia* advising Member States to take steps to ensure that the public are protected from exposure to aristolochic acids arising

from the deliberate use of *Aristolochia* species or as a result of confusion with other herbal ingredients (**Appendix 6**).

- ***Digitalis***
  Cases of serious cardiac arrhythmias were reported in the USA in 1997 following the accidental substitution of plaintain with Digitalis lanata.[35] Subsequent investigation revealed that large quantities of the contaminated plantain had been shipped to more than 150 manufacturers, distributors and retailers over a 2 year period**.**

- ***Podophyllum***
  Fourteen cases of podophyllum poisoning have been reported from Hong Kong following the inadvertent use of the roots *Podophyllum hexandrum* instead of *Gentiana* and *Clematis* species.[36] It is reported that this accidental substitution arose because of the apparent similarity in morphology of the roots.

- **Aconitum**
  Cases of cardiotoxicity resulting from the ingestion of *Aconitum* species used in TCM have been reported from Hong Kong.[37] In TCM, Aconitum rootstocks are processed by soaking or boiling them in water in order to hydrolyse the aconite alkaloids into their less toxic, aconine derivatives. Toxicity can, however, result when such processes are uncontrolled and unvalidated. In the UK, the internal use of Aconite is restricted to prescription only.

4.1.2 **Adulteration with heavy metals/ toxic elements and synthetic drugs**

The adulteration of ethnic medicines with heavy metals/ toxic elements and synthetic drugs continues to be a significant international problem. A comprehensive review has summarised test results on products and case histories of patients who had experienced toxic effects. [19] Similar findings continue to be reported. In most cases involving synthetic drugs they are undeclared in the product and only come to light when the user experiences adverse effects which are sufficiently serious to warrant medical intervention. Exposure to the undeclared drug is revealed in the subsequent investigation of the clinical case.

The situation with the heavy metals/toxic elements differs in that whilst these ingredients may arise from the plant ingredients themselves or be introduced as trace contaminants during processing they are frequently added intentionally and declared as ingredients within TCM and Asian medicine formulations.

The Chinese Pharmacopoeia, for example, includes monographs for:

- realgar (arsenic disulphide),
- calomel (mercurous chloride),
- cinnabaris (mercuric sulphide),
- hydrargyri oxydum rubrum (red mercuric oxide)

and lists formulations for nearly fifty products that include one or more of these substances. [38]

A survey from the US reported findings of widespread inconsistencies and adulterations in imported Asian medicines. Of 260 imported products tested, at least 83(32%) contained undeclared pharmaceuticals (most commonly ephedrine, chlorpheniramine, methyltestosterone and phenacetin) or heavy metals (lead, arsenic or mercury. [39] A more recent US survey has found evidence of a continuing problem with 10% of 500 OTC products testing positive for undeclared drugs and/or toxic levels of lead, mercury or arsenic. [40]

Elsewhere health departments have reported similar conclusions based on their findings. A survey conducted in Singapore, between 1990-1997 on TCM products has reported that 42 different products were found to contain excessive heavy metals (mercury, lead, arsenic) while 32 different TCM products were found to contain a total of 19 drugs.[41] In total, 93 cases of excessive toxic heavy metals and undeclared drugs were detected. The drugs detected included berberine, antihistamines (chlorheniramine, promethazine, cyproheptadine), non-steroidal anti-inflammatory drugs (diclofenac, indomethacin, ibuprofen), analgesic antipyretics (paracetamol, dipyrone), corticosteroids (prednisolone, dexamethasone, fluocinonide), sympathomimetics agents (ephedrine) bronchodilators (theophylline), diuretic (hydrochlothiazide) and the antidiabetic (phenformin).

In Taiwan, more than 20% of 2609 products were found to be adulterated with synthetic drugs, most commonly caffeine, paracetamol, indomethacin and hydrochlorthiazide. [42]

Recently, the Singapore Ministry of Health reported finding sildenafil in two Chinese proprietary medicines [43].

FDA recalled a herbal product after traces of chlordiazepoxide were found in the capsules. [44]

In 2001, the MCA reported presence of mercury (due to the inclusion of cinnabaris) in samples of the product Shugan Wan on the UK market (**Appendix 1**).

Examples of recent cases of toxicity associated with synthetic drugs being present in ethnic medicines include a case of poisoning in Hong Kong resulting from the use of a TCM product containing the anticonvulsants (phenytoin, carbamazepine and valproate). [45]

In 2000, the FDA issued a public health warning on five herbal products following adverse effects in patients. [46] The products were found to contain the antihyperglycaemic drugs, glibenclamide and phenformin.

In March 2001, the UK Medicines Control Agency reported a serious case of hypoglycaemic coma in a patient as a result of taking a TCM product, Xiaoke Wan, which contained the prescription drug, glibenclamide. [47]

Examples of reports of cases of toxicity associated with heavy metals in ethnic medicines include a patient from Taiwan who developed a unique syndrome of multiple renal tubular dysfunction after taking a Chinese herbal medicine contaminated with cadmium. [48] In the US two cases have been reported of alopecia and sensory polyneuropathy resulting from thallium in a TCM product. [49]

In the UK, cases have been reported of two patients with heavy metal intoxication from ingestion of an Indian remedy containing inorganic arsenic and mercury [50] and of a patient with lead poisoning after exposure to an Indian medicine containing toxic levels of lead, arsenic and mercury. [51]

In a case reported from Macau, death of a 13 year-old girl from arsenic poisoning has been linked with a Chinese herbal product, Niu Huang Chieh Tu Pien. [52]

During 2002, the MCA has issued warnings to the public on a number of potentially serious instances of prescription medicines being found in herbal products. These include, sildenafil, fenfluramine, alprazolam and warfarin **(Appendix 5)**.

Problems with corticosteroids in creams for use in various skin conditions continues to be a significant problem in the UK. In Spring 2002, six samples of topical cream taken from four tradional Chinese medicine outlets tested positive for illegal steroids. MCA issued a warning to the public **(Appendix 5)**.

4.2 Quality of regulated herbal products

Compared with conventional preparations, herbal medicinal products present a number of unique problems when quality aspects are considered. These arise because of the nature of the herbal ingredients, which are complex mixtures of constituents, and it is well documented that levels of plant constituents can vary considerably depending on environmental and genetic factors. Furthermore, the constituents responsible for the claimed therapeutic effects are frequently unknown or only partly explained and this precludes the level of control which can routinely be achieved with synthetic drug substances in conventional pharmaceuticals. The position is further complicated by the traditional practice of using combinations of herbal ingredients, and it is not uncommon to have as many as 5 herbal ingredients in one product.

Control of the starting materials is essential in order to ensure reproducible quality of herbal medicinal products. [2,4,53,54] The following aspects need to be considered in the control of starting materials.

4.2.1 **Authentication and Reproducibility of Herbal Ingredients**

The problems associated with unregulated herbal products, as illustrated above, highlight the public health issues that can arise when the herbal ingredients have not been authenticated correctly. Herbal ingredients must be accurately identified by macroscopical and microscopical comparison with authentic material or accurate descriptions of authentic herbs [54] It is essential that herbal ingredients are referred to by their binomial Latin names of genus and species; only permitted synonyms should be used. Even when correctly authenticated, it is important to realise that different batches of the same herbal ingredient may differ in quality due to a number of factors.

- *Adulteration/Substitution*
  Instances of herbal remedies adulterated with other plant material and even with conventional medicines have been discussed above. Reports of herbal products devoid of known active constituents have reinforced the need for adequate quality control of herbal remedies. The serious public health consequences of the substitution of herbal ingredients by toxic *Aristolochia* species have been highlighted above.

- *Microbial Contamination*
  Aerobic bacteria and fungi are normally present in plant material and may increase due to faulty growing, harvesting, storage or processing. Herbal ingredients, particularly those with high starch content may be prone to increased microbial growth. It is not uncommon for herbal ingredients to have aerobic bacteria present at 10^2–10^8 colony forming units per gram. Pathogenic organisms including *Enterobacter*, *Enterococcus*, *Clostridium*, *Pseudomonas*, *Shigella* and *Streptococcus* have been shown to contaminate herbal ingredients. The European Pharmacopoeia (Ph Eur) gives non-mandatory guidance on acceptable limits. [55]

- *Pesticides*
  Herbal ingredients, particularly those grown as cultivated crops, may be contaminated by DDT or other chlorinated hydrocarbons, organophosphates, carbamates or polychlorinated biphenyls. Limit tests are necessary for acceptable levels of pesticide contamination of herbal ingredients. The Ph Eur includes details of test methods together with mandatory limits for 34 potential pesticide residues. [55]

- *Fumigants*
  Ethylene oxide, methyl bromide and phosphine have been used to control pests which contaminate herbal ingredients. The use of ethylene oxide as a fumigant with herbal drugs is no longer permitted in Europe due to concerns about carcinogenic residues. There are concerns, however, that products imported from outside the EU may have been treated with this fumigant.

- *Toxic Metals*
  Lead, cadmium, mercury, thallium and arsenic have been shown to be contaminants of some herbal ingredients. Limit tests for such toxic metals may be needed for certain herbal ingredients.

- *Other Contaminants*
  Tests to limit other contaminants such as endotoxins, mycotoxins and radionuclides may need to be considered to ensure suitable quality for medicinal purposes.

5. HERB-DRUG INTERACTIONS

Limited information is available regarding interactions between herbal products and conventional medicines. However, awareness of this issue is increasing and the potential for drug-herb interactions has been discussed. [56-59]

Concerns have been raised in the literature about herbal medicines interfering with breast cancer treatment [60] and potential interactions between herbal products and cardiac drugs. [61]

Instances of drug interactions have been tentatively linked, retrospectively, to the concurrent use of herbal remedies. The rationale for such interactions is often difficult to explain if knowledge regarding the phytochemical constituents of the herbal product, their pharmacological activity and metabolism are poorly understood.

The emergence of significant problems associated with the ingestion of grapefruit juice concurrently with certain medicines has emphasised the fact that clinically relevant interactions between drugs and natural products (both herbs and foods) may occur. [62]

As with conventional drug interactions, herb-drug interactions may be pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions could result when a herbal drug and a conventional drug have similar or antagonistic pharmacological effects or adverse effects. These interactions are usually predictable from a knowledge of the pharmacology of the interacting herb and drug. Pharmacokinetic interactions could occur when the herb alters the absorption, distribution, metabolism or excretion of the drug. They are not easily predicted.

As with all potential drug interactions there are particular concerns when patients are stabilised on conventional medicines such as warfarin, digoxin, anticonvulsants (eg. phentoin) and cyclosporin known to have a narrow therapeutic window.

- ***St John's Wort***

  Since 1998 evidence has emerged from spontaneous reports and published case reports of the interactions between St John's Wort and certain prescribed medicines leading to a loss of or reduction in therapeutic effect of these prescribed medicines (see St John's Wort monograph).[63] Drugs that may be affected include indinavir, warfarin, ciclosporin, digoxin, theophylline and oral contraceptives. There have also been reports of increased serotonergic effects in patients taking St John's wort concurrently with selective serotonin reuptake inhibitors eg. sertraline, paroxetine. Results of drug interaction studies have provided some evidence that St John's Wort may induce some cytochrome P450 (CYP) drug metabolising enzymes in the liver as well as affecting P-glycoprotein (a transport protein). Regulatory Authorities throughout the EU and elsewhere have issued advice to patients and healthcare professionals **(Appendix 5).**

  In February 2000, the CSM released guidance to healthcare professionals and the general public regarding St John's Wort and prescribed medicines (**Appendix 5**). As a result all prescribed medicines likely to interact with St John's Wort have warnings included in their Patient Information Leaflets. Furthermore, following a voluntary agreement with the herbal sector, all unlicensed products containing St John's Wort carry label warnings advising patients to seek advice if they are taking prescribed medicines.

Unlike St John's Wort, the evidence and understanding of most drug-herb interactions is limited. 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 adverse effects.

For example, herbs containing substantial levels of coumarins may potentially increase blood coagulation time if taken in large doses. 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 and 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 plants such as liquorice.

Examples of potential drug-herb interactions are included in **Table 3**.

- **Interactions of herbal products in therapeutic drug monitoring**

  Examples have also come to light where herbal medicinal products cross-react with diagnostic markers in therapeutic drug monitoring. Recent examples involved a Chinese medicine and Eletherococcus where the constituents cross-reacted with digoxin assays. [58]

6. PRECAUTIONS IN SPECIFIC PATIENT GROUPS

6.1 Pregnant/Breast-feeding mothers

Few conventional medicines have been established as safe to take during pregnancy and it is generally recognised that no medicine should be taken unless the benefit to the mother outweighs any possible risk to the foetus. This rule should also be applied to herbal medicinal products. However, herbal products are often promoted to the public as being "natural" and completely "safe" alternatives to conventional medicines.

Table 4 lists some herbal ingredients that specifically should be avoided or used with caution during pregnancy. As with conventional medicines, no herbal products should be taken during pregnancy unless the benefit outweighs the potential risk.

- *Volatile Oils*
  Many herbs are traditionally reputed to be abortifacient and for some this reputation can be attributed to their volatile oil component.[6] A number of volatile oils are irritant to the genito-urinary tract if ingested and may induce uterine contractions. Herbs that contain irritant volatile oils include ground ivy, juniper, parsley, pennyroyal, sage, tansy and yarrow. Some of these oils contain the terpenoid constituent, thujone, which is known to be abortifacient. Pennyroyal oil also contains the hepatotoxic terpenoid constituent, pulegone. A case of liver failure in a woman who ingested pennyroyal oil as an abortifacient has been documented.[64]

- *Uteroactivity*
  A stimulant or spasmolytic action on uterine muscle has been documented for some herbal ingredients including blue cohosh, burdock, fenugreek, golden seal, hawthorn, jamaica dogwood, motherwort, nettle, raspberry, and vervain.

- *Herbal Teas*
  Increased awareness of the harmful effects associated with excessive tea and coffee consumption has prompted many individuals to switch to herbal teas. Whilst some herbal teas may offer pleasant alternatives to tea and coffee, some contain pharmacologically active herbal ingredients, which may have unpredictable effects depending on the quantity of tea consumed and strength of the brew. Some herbal teas contain laxative herbal ingredients such as senna, frangula, and cascara. In general stimulant laxative preparations are not recommended during pregnancy and the use of unstandardised laxative preparations is particularly unsuitable. A case of hepatotoxicity in a newborn baby has been documented in which the mother consumed a herbal tea during pregnancy as an expectorant.[65] Following analysis the herbal tea was reported to contain pyrrolizidine alkaloids which are known to be hepatotoxic.

6.2 Breast-feeding mothers

A drug substance taken by a breast-feeding 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 breast-feeding. Much less information exists for herbal ingredients, and generally the use of herbal remedies is not recommended during lactation.

6.3 Paediatric Use

Herbal remedies have traditionally been used to treat both adults and children. Herbal remedies may offer a milder alternative to some conventional medicines, although the suitability of a herbal remedy needs to be considered with respect to quality, safety and efficacy. Herbal remedies should be used with caution in children and medical advice should be sought if in doubt. Chamomile is a popular remedy used to treat teething pains in babies. However, chamomile is known to contain allergenic sesquiterpene lactones and should therefore be used with caution. The administration of herbal teas to children needs to be considered carefully and professional advice may be needed. [66]

Other patient groups

6.4 Elderly

A recent review has considered the evidence available on the use of a number of herbal medicinal products by the elderly (St John's Wort, valerian, ginkgo, horse chestnut, saw palmetto and yohimbe).[67] Whilst the treatments may offer considerable benefits for a range of conditions the review raised the need for caution when herbal medicinal products are used by the elderly particularly with regard to potential drug-herb interactions and possible side-effects.

6.5 Patients with cardiovascular disease

Concerns have been raised about herbal medicinal products for cardiovascular disease, in particular, the lack of scientific assessment and the potential for toxic effects and major drug-herb interactions. [68]

6.6 Perioperative use

The need for patients to discontinue herbal medicinal products prior to surgery has recently been proposed.[69] The authors considered eight commonly used herbal medicinal products (echinacea, ephedra, garlic, ginkgo, ginseng, kava, St John's Wort, valerian). On the evidence available they concluded that the potential existed for direct pharmacological effects, pharmacodynamic interactions and pharmacokinetic interactions. The need for physicians to have a clear understanding of the herbal medicinal products being used by patients and to take a detailed history was highlighted.

The American Society of Anaesthesiologists(ASA) has advised patients to tell their doctor if they are taking herbal products before surgery and has reported that a number of anaesthesiologists have reported significant changes in heart rate or blood pressure in some patients who have been taking herbal medicinal products including St John's Wort, ginkgo and ginseng. [70]

MCA is currently investigating a serious adverse reaction associated with the use of ginkgo prior to surgery. In this case, the patient who was undergoing hip replacement experienced uncontrolled bleeding thought to be related to the use of ginkgo.

7. REPORTING OF ADVERSE REACTIONS TO HERBAL MEDICINAL PRODUCTS

7.1 It is essential that information on the risks associated with the use of herbal products is systematically collected and analysed in order to protect public health.

7.2 In 1996, the UK the MCA extended its 'Yellow Card Scheme' to include reporting of suspected adverse reactions to unlicensed herbal products. This followed a report from Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal remedies. Twenty-one cases of liver toxicity, including two deaths, were associated with the use of TCM. [5]

7.3 The need to further improve pharmacovigilance on herbal products was highlighted in a study of patients' attitudes to reporting adverse reactions. [3] The study found that patients would be less likely to consult their doctor for suspected drug reactions (minor or severe) to herbal remedies than for similar adverse reactions to a conventional over-the-counter remedy. This illustrates the need for greater public awareness that adverse reactions can occur and that such reactions should be reported. It also highlights the need for healthcare professionals to take a detailed medical history including use of herbal products and to be aware that patients may be reluctant to provide information.

7.4 The Uppsala Monitoring Centre of the World Health Organisation plays an important role in the international monitoring of adverse health effects associated with herbal medicines. [71] The Centre has carried out an analysis of the suspected adverse reactions to herbal medicines reported over a period of 20 years. Of the 2487 case reports reported to occur with single-ingredient herbal products, 21 (0.8%) the suspected adverse reaction had a fatal outcome. Three of these reports concerned intestinal perforation after administration of a Senna-containing laxative, presumed to be prior to X-ray examination because of intestinal pathology. Three reports concerned respiratory failure in association with the use of Psyllium mucilloid-containing products and three other of respiratory failure in association with Ispaghula husk. One patient had an anaphylactic shock after the injection of a Horse Chestnut extract. In the remaining cases no pattern was recognizable. The Centre has highlighted the need for improved reporting in particular with regard to the precise identity and composition of the products.

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Table 2: Examples of Potential Adverse Effects of Herbal Ingredients

Herb	*Adverse effect*	*Reasons/Comments*
Agnus Castus	Allergic reactions	—
Alfalfa	Systemic lupus erythematosus syndrome	Canavanine, toxic amino acid
Aloes	Purgative, irritant to GI tract	Anthraquinones
Angelica	Phototoxic dermatitis	Furanocoumarins
Aniseed	Contact dermatitis	Anethole in volatile oil
Apricot[1]	Cyanide poisoning, seed	Cyanogenetic glycosides
Arnica[1]	Dermatitis, irritant to GI tract	Sesquiterpene lactones
Artichoke	Allergenic, dermatitis	Sesquiterpene lactones
Asafoetida	Dermatitis, irritant	Gum, related species
Bayberry	Carcinogenic to rats	—
Blue Flag	Nausea, vomiting, irritant to GI tract and eyes	Fresh root, furfural (volatile oil)
Bogbean	Purgative, vomiting	In large doses
Boldo	Toxicity, irritant	Volatile oil
Boneset	Dermatitis, cytotoxic	Sesquiterpene lactones
Borage[1]	Genotoxic, carcinogenic, hepatotoxic	Pyrrolizidine alkaloids
Broom	Cardiac depressant	Sparteine (alkaloid)
Buchu	Irritant to GI tract, kidney	Volatile oil
Calamus[1]	Carcinogenic, nephrotoxic, convulsions	β-Asarone in oil
Capsicum	Irritant	Capsaicinoids
Cascara	Purgative, irritant to GI tract	Anthraquinones
Cassia	Allergenic, irritant	Cinnamaldehyde in volatile oil
Celery	Phototoxic, dermatitis	Furanocoumarins
Cereus	Irritant to GI tract	Fresh juice
Chamomile, German	Allergic reactions	Sesquiterpene lactones
Chamomile, Roman	Allergic reactions	Sesquiterpene lactones
Chaparral	Dermatitis, hepatotoxic	Lignans
Cinnamon	Allergenic, irritant	Cinnamaldehyde in volatile oil
Clove	Irritant	Eugenol in volatile oil
Cohosh, Black	Nausea, vomiting	High doses
Cohosh, Blue	Irritant to GI tract	Seeds poisonous
Cola	Sleeplessness, anxiety, tremor	Caffeine
Coltsfoot[1]	Genotoxic, carcinogenic, hepatotoxic	Pyrrolizidine alkaloids
Comfrey[1]	Genotoxic, carcinogenic, hepatotoxic	Pyrrolizidine alkaloids
Corn Silk	Allergenic, dermatitis	—
Cowslip	Allergenic	Quinones
Damiana	Convulsions	High dose (one report only), quinones, cyanogenetic glycosides
Dandelion	Allergenic, dermatitis	Sesquiterpene lactones
Echinacea	Allergenic, irritant	Polysaccharide
Elecampane	Allergenic, irritant	Sesquiterpene lactones
Eucalyptus	Nausea, vomiting	Oil
Evening Primrose Oil	Mild indigestion, increased risk of epilepsy	Schizophrenic patients on phenothiazines
Eyebright	Mental confusion, raised intraocular pressure	Tincture

Feverfew	Allergenic, dermatitis	Sesquiterpene lactones
Frangula	Purgative, irritant to GI tract	Anthraquinones
Fucus	Hyperthyroidism	Iodine content
Garlic	Irritant to GI tract, dermatitis	Sulphides
Ginkgo	Gastric upset, headache	—
Ginseng	Mastalgia, vaginal bleeding , insomnia	Various effects, *see* Monographs
Golden Seal	Gastric upset	Berberine, potentially poisonous
Gravel Root[1]	Genotoxic, carcinogenic, hepatotoxic	Pyrrolizidine alkaloids
Ground Ivy	Irritant to GI tract, kidneys	Pulegone in volatile oil
Guaiacum	Allergenic, dermatitis	Lignans
Hops	Allergenic, dermatitis	Oleo-resin
Horehound, White	Dermatitis, irritant	Plant juice
Horse-chestnut	Nephrotoxic	Aescin
Horseradish	Allergenic, irritant	Glucosinolates
Hydrangea	Dermatitis, irritant to GI tract	—
Hydrocotyle	Phototoxic, dermatitis	—
Ispaghula	Oesophageal obstruction, flatulence	If swallowed dry
Jamaica Dogwood	Irritant, numbness, tremors	High doses
Juniper	Irritant, abortifacient	Volatile oil, confusion with savin
Lady's Slipper	Allergenic, dermatitis, hallucinations	—
Liferoot[1]	Genotoxic, carcinogenic, hepatotoxic	Pyrrolizidine alkaloids
Liquorice	Hyperaldosteronism	Excessive ingestion
Lobelia	Nausea, vomiting, diarrhoea	Lobeline (alkaloid)
Maté	Sleeplessness, anxiety, tremor	Caffeine
Mistletoe	Hepatitis, hypotension, poisonous	Mixed herbal preparation
Motherwort	Phototoxic dermatitis	Volatile oil
Nettle	Irritant	Amines
Parsley	Irritant, hepatitis, phototoxic, abortifacient	Apiole in volatile oil, excessive ingestion
Pennyroyal	Irritant, nephrotoxic, hepatotoxic	Pulegone in volatile oil
Pilewort[1]	Irritant	Protoanemonin
Plantain	Allergenic, dermatitis, irritant	Mustard-type oil
Pleurisy Root	Dermatitis, irritant, cardiac activity	Cardenolides
Pokeroot	Mitogenic, toxic, nausea, vomiting, cramp	Lectins
Prickly Ash, Southern	Toxic to animals	—
Pulsatilla[1]	Allergenic, irritant	Protanemonin
Queen's Delight[1]	Irritant to GI tract	Diterpenes
Red Clover	Oestrogenic	Isoflavonoids
Rhubarb	Purgative, irritant to GI tract	Anthraquinones
Rosemary	Convulsions	Camphor in volatile oil
Sage	Toxic, convulsant	Thujone, camphor in volatile oil
Sassafras[1]	Carcinogenic, genotoxic	Safrole in volatile oil
Scullcap	Hepatotoxicity	Mixed product; adulteration with *Teucrium* spp.
Senega	Irritant to GI tract	Saponins
Senna	Purgative, irritant to GI tract	Anthraquinones
Shepherd's Purse	Irritant	Isothiocyanates
Skunk Cabbage	Itch, inflammation	—
Squill	Irritant, cardioactive	Saponins
St. John's Wort	Phototoxic	Hypericin
Tansy[1]	Severe gastritis, convulsions	Thujone in volatile oil
Thyme	Irritant to GI tract	Thymol in volatile oil
Wild Carrot	Phototoxic, dermatitis	Furanocoumarins

Yarrow	Allergenic, dermatitis	Sesquiterpene lactones
Yellow Dock	Purgative, irritant to G1 tract	Anthraquinones

[1] Not recommended for internal use

Table 3: Examples of Potential Drug/Herb Interactions

Drug/ Therapeutic Category Affected	*Herbal Ingredients Interacting*	*Possible Effects*
Gastrointestinal System		
Antacids, ulcer-healing drugs	Herbal ingredients irritant to gastro-intestinal tract.	Exacerbation of symptoms Risk of systemic side-effects
Antidiarrhoeal drugs	Herbal ingredients with laxative activity.	Antagonism
Laxatives	Herbal ingredients with laxative activity.	Potentiation; increased risk of side-effects
Cardiovascular system		
Cardiac glycosides	Cardioactive herbal ingredients.	Potentiation; increased risk of side-effects
Diuretics	Herbal ingredientswith diuretic activity. Herbal ingredients with hypotensive activity.	Potentiation; increased risk of hypokalaemia Difficulty in controlling diuresis; hypertension
Anti-arrhythmic activity	Cardioactive herbal ingredients Herbal ingredients with diuretic activity.	Interference/antagonism with existing therapy Antagonism if hypokalaemia occurs
Beta-adrenoceptor blocking drugs	Cardioactive herbal ingredients. Herbal ingredients with significant levels of amines/ sympathomimetic activity.	Potential antagonism Potential risk of severe hypertension
Antihypertensive therapy	Herbal ingredients with hypertensive activity. Herbal ingredients with mineralocorticoid activity, e.g. bayberry, liquorice. Herbal ingredients with hypotensive activity. Herbal ingredients with significant levels of amines/sympathomimetic activity. Herbal ingredients with diuretic activity.	Antagonism Antagonism Potentiation Antagonism Risk of potentiation/ interference with existing therapy
Lipid-lowering drugs	Herbal ingredients with hypolipidaemic activity.	Additive effect
Cardiovascular System (*continued*)		
Nitrates and calcium-channel blockers	Cardioactive ingredients. Blue cohosh Herbal ingredients with hypertensive activity. Herbal ingredients with anticholinergic activity	Interference with therapy Interference with therapy Antagonism Reduced sublingual absorption of glyceryl trinitrate
Sympathomimetics	Herbal ingredients with significant sympathomimetic amines. Herbal ingredients with hypertensive activity. Herbal ingredients with hypotensive activity.	Potentiation; increased risk of hypertension Increased risk of hypertension Antagonism
Anticoagulants	Herbal ingredients with coagulant/ anticoagulant activity. Herbal ingredients with coumarins Herbal ingredients with significant	Risk of potentiation or antagonism Risk of potentiation Risk of potentiation Raised INR reported in 2 patients receiving warfarin Plasma

	salicylate levels. Garlic Horse-chestnut	protein binding
Respiratory System	Herbal ingredients that are potentially allergenic.	Risk of allergic reaction
Terfenadine	Cardioactive herbal ingredients. Herbal ingredients with diuretic activity.	May increase arrhythmogenic potential of terfenadine Electrolyte imbalance may increase arrhythmogenic potential of terfenadine
Allergic disorders	Herbal ingredients claimed to have sedative activity.	Potentiation of drowsiness associated with antihistamines
Central Nervous System		
Hypnotics and anxiolytics	Herbal ingredients claimed to have sedative activity.	Potentiation
Stimulants	Ginseng	Increased risk of ginseng side-effects
Antipsychotics	Herbal ingredients with diuretic activity. Herbal ingredients with anticholinergic activity Evening Primrose	Potentiation of lithium therapy; increased risk of toxicity; diuretics reported to reduce lithium clearance Risk of interference with therapy; anticholinergic drug reported to reduce plasma-phenothiazine concentrations Potential risk of seizure
Antidepressants	Herbal ingredients with sympathomimetic amines. . Ginseng Herbal ingredients containing tryptophan. White Horehound Herbal ingredients with sedative activity. Hops St. John's Wort	Risk of hypertensive crisis with monoamine-oxidase inhibitors (MAOIs) Suspected phenelzine interaction Risk of CNS excitation and confusional states with MAOIs Hydroxytryptamine antagonism, *in vivo* May potentiate sedative side-effects Antagonism; contra-indicated in patients with depressive illness
Central Nervous System (*continued*)		
Drugs used in nausea and vertigo	Herbal ingredients with sedative activity. Herbal ingredients with anticholinergic activity	May potentiate sedative side-effects Antagonism
Analgesics	Herbal ingredients with diuretic activity. Herbal ingredients with corticosteroid activity, e.g. bayberry, liquorice. Herbal ingredients with sedative activity.	Increased risk of toxicity with anti-inflammatory analgesics Possible reduction in plasma-aspirin concentrations May potentiate sedative side-effects
Antiepileptics	Herbal ingredients with sedative activity. Borage Evening primrose oil Ground ivy Sage Herbal ingredients with significant salicylate levels (Meadowsweet, Poplar, Willow) Herbal ingredients with significant folic acid levels	May potentiate sedative side-effects May increase risk of seizure May increase risk of seizure May increase risk of seizure Transient potentiation of phenytoin therapy may occur Plasma-phenytoin concentration may be reduced
Drugs for parkinsonism	Herbal ingredients with anticholinergic activity Herbal ingredients with cholinergic activity	Potentiation; increased risk of side-effects 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. Herbal ingredients with diuretic activity.	Potentiation/ antagonism of activity Antagonism
Drugs for hypo- and hyperthyroidism	Herbal ingredients with significant iodine content e.g. Fucus Horseradish, Myrrh	Interference with therapy Interference with therapy
Corticosteroids	Herbal ingredients with diuretic activity. Herbal ingredients with corticosteroid activity e.g. Bayberry, Liquorice.	Risk of increased potassium loss Increased risk of side-effects e.g. water and sodium retention
Sex hormones	Herbal ingredients with hormonal activity.	Possible interaction with existing therapy
Obstetrics and Gynaecology		
Oral contraceptives	Herbal ingredients with hormonal activity.	Possible interaction with existing therapy; may reduce effectiveness of oral contraceptive
Malignant Disease and Immunosuppression		
Methotrexate	Herbal ingredients with significant salicylate levels.	Increased risk of toxicity
Drugs affecting immune response	Herbal ingredients with immunostimulant activity.	Potentiation or antagonism
Musculoskeletal and Joint Diseases		
Systemic lupus erythematosus	Alfalfa	Antagonism; contra-indicated
Probenecid	Herbal ingredients with significant salicylate levels.	Risk of inhibition of probenecid
Eye		
Acetazolamide	Herbal ingredients with significant salicylate levels.	Increased risk of toxicity
Skin	Herbal ingredients with potential allergenic activity. Herbal ingredients with phototoxic activity.	Allergic reaction; exacerbation of existing symptoms Phototoxic reaction; exacerbation of existing symptoms
Anaesthetics		
General anaesthetics	Herbal ingredients with hypotensive activity.	Potentiation of hypotensive effect
Competitive muscle relaxants	Herbal ingredients with diuretic activity.	Risk of potentiation if hypokalaemia occurs
Depolarising muscle relaxants	Cardioactive herbal ingredients.	Risk of arrhythmias

Table 4: Examples of Herbal Ingredients Best Avoided or used with Caution during Pregnancy

Herb	***Effect***
Agnus Castus	Hormonal action
Aloes	Cathartic, reputed abortifacient
Apricot	Cyanide toxicity
Asafoetida	Reputed abortifacient and to affect menstrual cycle
Avens	Reputed to affect menstrual cycle
Blue Flag	Irritant oil
Bogbean	Irritant, possible purgative
Boldo	Irritant oil
Boneset	Cytotoxic constituents (related species)
Borage	Pyrrolizidine alkaloids
Broom	Sparteine is oxytoxic
Buchu	Irritant oil
Burdock	Uterine stimulant, *in vivo*
Calendula	Reputed to affect menstrual cycle, uterine stimulant, *in vitro*
Cascara	Anthraquinones, non-standardised preparations to be avoided
Chamomile, German	Reputed to affect menstrual cycle, uterine stimulant with excessive use
Chamomile, Roman	Reputed abortifacient and to affect menstrual cycle with excessive use
Chaparral	Uterine activity, hepatotoxic
Cohosh, Black	Uterine oestrogen receptor binding *in vitro*
Cohosh, Blue	Reputed abortifacient and to affect menstrual cycle
Cola	Caffeine, consumption should be restricted
Coltsfoot	Pyrrolizidine alkaloids
Comfrey	Pyrrolizidine alkaloids
Cornsilk	Uterine stimulant, *in vivo*
Damiana	Cyanogenetic glycosides, risk of cyanide toxicity in high doses
Devil's Claw	Oxytoxic
Eucalyptus	Oil should not be taken internally during pregnancy
Euphorbia	Smooth muscle activity, *in vitro*
Fenugreek	Oxytoxic, uterine stimulant, *in vitro*
Feverfew	Reputed abortifacient and to affect menstrual cycle
Frangula	Anthraquinones, non-standardised preparations to be avoided
Fucus	Thyroid gland activity, possible heavy metal contamination
Gentian	Reputed to affect menstrual cycle
Ginseng, Eleutherococcus	Hormonal activity
Ginseng, Panax	Hormonal activity
Golden Seal	Alkaloids with uterine stimulant activity, *in vitro*
Ground Ivy	Irritant oil
Hawthorn	Uterine activity, *in vivo*, *in vitro*
Hops	Uterine activity, *in vitro*
Horehound, Black	Reputed to affect menstrual cycle
Horehound, White	Reputed abortifacient and to affect menstrual cycle
Horseradish	Irritant oil; avoid excessive ingestion
Hydrocotyle	Reputed abortifacient and to affect menstrual cycle

Jamaica Dogwood	Uterine activity, *in vitro*, *in vivo;* irritant
Juniper	Reputed abortifacient and to affect menstrual cycle. Confusion over whether oil is toxic
Liferoot	Pyrrolizidine alkaloids
Liquorice	Oestrogenic activity, reputed abortifacient
Lobelia	Lobeline, toxicity
Maté	Caffeine, consumption should be restricted
Meadowsweet	Uterine activity, *in vitro*
Mistletoe	Toxic constituents, uterine stimulant, animal
Motherwort	Uterine activity, *in vitro*, reputed to affect menstrual cycle
Myrrh	Reputed to affect menstrual cycle
Nettle	Reputed abortifacient and to affect menstrual cycle
Passionflower	Harman, harmaline uterine stimulants, animal
Pennyroyal	Abortifacient, irritant oil (pulegone)
Plantain	Uterine activity, *in vitro*; laxative
Pleurisy Root	Uterine activity, *in vivo;* cardioactive constituents
Pokeroot	Toxic constituents, uterine stimulant, reputed to affect menstrual cycle
Poplar	Conflicting reports over use of aspirin in pregnancy; salicylates excreted in breast milk may cause rashes in babies
Prickly Ash, Northern	Pharmacologically active alkaloids and coumarins
Prickly Ash, Southern	Pharmacologically active alkaloids
Pulsatilla	Reputed to affect menstrual cycle, uterine activity,, *in vitro*, *in vivo;* irritant (fresh plant)
Queen's Delight	Irritant diterpenes
Raspberry	Uterine activity, *in vitro*, traditional use to ease parturition
Red Clover	Oestrogenic activity
Rhubarb	Anthraquinones, non-standardised preparations to be avoided
Sassafras	Abortifacient (oil), hepatotoxic (safrole)
Scullcap	Traditional use to eliminate afterbirth and promote menstruation; potential hepatotoxicity
Senna	Anthraquinones, non-standardised preparations to be avoided
Shepherd's Purse	Reputed abortifacient and to affect menstrual cycle
Skunk Cabbage	Reputed to affect menstrual cycle
Squill	Reputed abortifacient and to affect menstrual cycle
St. John's Wort	Slight uterine activity, *in vitro*
Tansy	Uterine activity, abortifacient (thujone in oil)
Uva-Ursi	Large doses, oxytocic
Vervain	Reputed abortifacient, oxytocic, uteroactivity *in vivo*
Wild Carrot	Oestrogenic activity, irritant oil
Willow	Conflicting reports over use of aspirin in pregnancy; salicylates excreted in breast milk may cause rashes in babies
Yarrow	Reputed abortifacient and to affect menstrual cycle (thujone in oil)
Yellow Dock	Anthraquinones, non-standardised preparations to be avoided

APPENDICES

Appendix 1: Traditional Ethnic Medicines: Public Health and Compliance with Medicines Law, November 2001

Appendix 2: Review of Herbal Ingredients for use in Unlicensed Herbal Medicinal Products. September 2001

Appendix 3: MCA Press Releases: Concern over Quality and Safety Standards of Traditional Chinese Medicines, September 2001

Appendix 4: MCA Notifications on Safety of Kava-kava products, December 2001-July 2002

Appendix 5: MCA Herbal Safety News: July 2002

- Senecio
- Warfarin/Alprazolam
- Fenfluramine
- Sildenafil
- Topical Creams containing steroids
- Aristolochia
- St John's Wort

Appendix 6: EMEA Position Paper on the Risks Associated with the use of Herbal Products containing *Aristolochia* species