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Review Article

The safe usage of herbal medicines: counter-indications, cross-reactivity and toxicity

I. E. Cock[a,b*]

[a]*School of Natural Sciences, Nathan Campus, Griffith University, 170 Kessels Rd, Nathan, Brisbane, Queensland 4111, Australia*
[b]*Environmental Futures Research Institute, Nathan Campus, Griffith University, 170 Kessels Rd, Nathan, Brisbane, Queensland 4111, Australia*

ABSTRACT

Background: Plants have been used therapeutically for thousands of years and continue to be the main treatment modality for a large percentage of the world's population. Furthermore, herbal medicine usage is increasing in Western countries as complementary (and sometimes alternative) treatments in conjunction with allopathic medicine. At the same time, the usage of allopathic medicines is being increasingly incorporated into the medicinal systems of developing countries, often resulting in the concurrent usage of both systems. **Importance of the Study:** Despite the widespread usage in developing countries and the trend of increasing medicinal plant usage in Western countries, herbal medicines remain understudied and there are misunderstandings amongst users and practitioners about the safe usage of these medications, particularly when used in conjunction with other medicines. Herbal medicines are generally not held to the same rigorous standards as allopathic medicines. There is usually a lack of industry regulation and manufacturing standards and guidelines, resulting in inferior (or unsafe) medicines being sold to consumers. Similarly, there is a lack of understanding amongst many medical practitioners of both traditional and allopathic medicine systems of how drugs from the two systems can be safely used together. **Aim:** The aim of this review is to summarise the current knowledge about herbal medicines and how they can be used safely, with the aim of not only highlighting some of the unsafe uses, but also to stimulate further research. I have also aimed to highlight the need for greater regulation and standardisation of herbal medicines.

Key words: Drug interactions, pharmacokinetic, pharmacodynamics, drug metabolism, cytochrome P450, side effects, complementary and alternative medicine, quality control.

INTRODUCTION

Before the advances of modern medicine, civilizations confronted with illness and disease discovered a wealth of useful therapeutic agents from within the plant kingdom. The earliest records outlining man's usage of plant medications are more than 6000 years old. Sumerian clay tablets (4000 BC) detail 1000 medicinal plants and plant remedies.[1,2] The Pun-tsao, a Chinese record of thousands of herbal cures dates to 2500 BC. The Hippocratic Corpus (a collection of medical texts of herbal remedies) by Greek physician Hippocrates was recorded in the late fifth century BC and the Roman writings De Materia Medica by Dioscorides, document more than 600 plant species with medicinal value.[2]

Many developing cultures (particularly Asian and African) have assimilated herbal medicine into their primary modality of health care[3] and herbal medications remain an important component of their medicinal systems. By documenting and practicing traditional medicine these cultures have accumulated comprehensive ethnobotanical data and improved their skills over time. Ayuvedic medicine is still commonly practiced within India with an estimated 85% of Indians still using crude plant formulations for the treatment of various diseases and ailments.[4]

Even the allopathic/Western medicinal systems practiced in developed countries owe much to our understanding of plant based remedies. (Table 1) lists some commonly

Corresponding Address
Tel.: +61 7 37357637; fax: +61 7 37355282.
E-mail address: I.Cock@griffith.edu.au (I. E. Cock).
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used allopathic drugs derived from plants. The listed drugs have widespread medicinal uses including as analgesics, central nervous system stimulants/depressants, antimalarial drugs, antiseptics, anti-tumour and anti-cancer agents, cardiac drugs, cholesterol lowering agents, anti-diabetic agents, as well as psychoactives. Indeed, it has been estimated that approximately 25% of all prescription drugs currently in use are originally derived from plants.[5-7] Furthermore, approximately 75% of new anticancer drugs marketed between 1981 and 2006 were derived from plant compounds.[6]

Despite the value of plants as medicinal agents, it is important that users and prescribers be aware of the potentially harmful effects of herbal drugs. Indeed, it has often been stated that medicines are toxins which are taken at lower, therapeutic doses. Therefore, even when a particular medicine has a medicinally desirable effect at a given dose, it may be toxic at higher doses. An example is the cardiac glycoside digoxin which is present in plants of the genus Digitalis. Digoxin is an anti-arrhythmic agent which is used to treat a variety of cardiac conditions. It is a very useful drug in therapeutic doses. At higher doses it can cause bradycardia or even block contraction and may be life threatening.[8] This dosage effect is also true of commercial pharmaceuticals. Acetaminophen (paracetemol) is an effective analgesic at therapeutic doses, yet at high doses it is hepatotoxic and a common cause of liver failure in developed countries.[9] However, commercial pharmaceuticals such as acetaminophen are generally well characterised and studied, and subject to quality control. The same may not be true of herbal medicines, with different preparations containing varying quantities of the active ingredient, as well as impurities, some of which may also be detrimental. It is therefore important that medicinal plants and the products derived from them need to be more completely characterised in terms of their composition. Furthermore, herbal medicines need to be thoroughly studied and their mechanisms of action determined so that we understand their potential for toxicity and their cross-reactivity with other drugs.

Often people who use plant based medicines self-diagnose their conditions and prescribe plant preparations for themselves. An incorrect diagnosis or choice of herbal medicine may be dangerous as plant medicines often contain multiple bioactive compounds. Therefore an inappropriate or even dangerous remedy may be prescribed. Many drugs have altered effects or efficacies in the presence of other drugs. For example, St Johns wort is a perennial herb indigenous to Europe which is often used to treat depression.[10] It is well established that administration of St Johns wort will counteract the effects of warfarin.[11] Warfarin is an anticoagulant that is often prescribed for preventing thrombosis and embolism. Therefore the counteracting effect of St Johns wort in patients prescribed warfarin could potentially have fatal results. Furthermore, a medicine that has a desirable effect in one tissue may in fact also have an undesirable effect in other tissues. There have been limited scientific studies into the safety and effectiveness of most herbal medicine preparations. It is necessary to understand the mechanism of action and cross-reactivity of any drug before using multiple drugs or preparations in combination. Such studies are routinely undertaken prior to allopathic drugs being released onto the market, yet no such requirement currently exists for natural therapeutics.

In contrast to allopathic medicines, many natural medicines are often not effectively regulated. Thus, different herbal preparations will contain different types and quantities of phytochemicals. Whilst some herbal medicines contain standardized quantities of one (or even several phytochemicals) other chemicals within the preparation are often not standardized. For example, commercially available Aloe vera juices may note levels of several important phytochemicals (e.g. Aloe emodin, barbaloin) without fully detailing the levels of other important components. As the levels and ratios of various components in Aloe vera juices have profound effects on their bioactivity,[12] it is important that the levels of these components are known.

Precautions also need to be taken in patients with specialized circumstances (e.g. in pregnant women). In an effort to avoid drugs, pregnant women often use herbal medicines as they believe them to be harmless. During pregnancy, the maternal bloodstream is shared with the fetal bloodstream. Thus toxic chemicals ingested by the mother will be shared with the fetus. As the fetus generally will not have developed the same tolerances as the mother, acute toxicity may develop in the fetus. Furthermore, some chemicals (including those found in herbal medicines) may be mutagenic. Such chemicals would be likely to have more profound effects in a developing fetus than to the mother. Many women quite sensibly quit smoking and drinking alcohol during pregnancy for this very reason, without considering the effects of the herbal medicines they are also taking. Similarly, toxic compounds may be present in the breast milk of women taking herbal medicines. The same precautions should be exercised by breastfeeding women as during pregnancy. Children, elderly people, immuno-compromised individuals, and those suffering severe allergies to specific drugs are other examples of people who should exercise caution

Table 1: A sample of plant derived drugs commonly used in allopathic medicine.			
Acetyldigoxin	Colchicine	Khellin	Rotenone
Adoniside	Convallotoxin	Lanatosides A, B, C	Rotundine
Aescin	Curcumin	Lobeline	Salicin
Aesculetin	Cynarin	Lovostatin	Santonin
Agrimophol	Danthron	Morphine	Scillarin A
Ajmalicine	Deserpidine	Neoandrographolide	Scopolamine
Allantoin	Deslanoside	Noscapine	Sennosides A & B
Allyl isothiocyanate	Digitalin	Ouabain	Silymarin
Andrographolide	Digitoxin	Papain	Stevioside
Anisodamine	Digoxin	Phyllodulcin	Strychnine
Anisodine	Emetine	Physostigmine	Teniposide
Arecoline	Ephedrine	Picrotoxin	Tetrahydropalmatine
Asiaticoside	Etoposide	Pilocarpine	Theobromine
Atropine	Gitalin	Podophyllotoxin	Theophylline
Berberine	Glaucaroubin	Protoveratrines A & B	Trichosanthin
Bergenin	Glycyrrhizin	Pseudoephedrine	Tubocurarine
Bromelain	Gossypol	Quinine	Valepotriates
Caffeine	Hemsleyadin	Quisqualic Acid	Vincamine
(+)-Catechin	Hydrastine	Rescinnamine	Xanthotoxin
Chymopapain	Hyoscamine	Reserpine	Yohimbine
Cocaine	Kainic Acid	Rhomitoxin	Yuanhuacine
Codeine	Kawain	Rorifone	Yuanhuadine

with natural medications, as indeed they should for any medication. This study seeks to highlight some of the factors that users, prescribers and researchers of herbal medicines should be aware of. Furthermore, I aim to highlight the need for studies to examine the efficacy and standardisation of herbal medicines, together with their potential side effects and ways to avoid these effects. Only through rigorous testing and standardisation similar to that required for allopathic medicines will the safety and efficacy of herbal medicines be assured and the usage more widely accepted.

POTENTIALLY HARMFUL COMPONENTS OF HERBAL MEDICINES

Harmful constituents may be introduced into herbal medicines unintentionally as contaminants, or intentionally as adulterants. Many commercial herbal medications are produced in countries where the manufacturing quality control standards and processes are inadequate or below the standards of some of the countries where they are subsequently marketed. Often there is considerable variation between the composition of different preparation batches, even from a single manufacturer. This variation may be even more pronounced when preparations from different manufacturers, often using different production processes, are compared. Furthermore, the amount of adulterant (when present) may not be adequately recorded and indicated on the medicines packaging. Indeed, some manufacturers may not report the adulterant at all.

Contamination with Heavy Metals

Contamination of herbal medicines with heavy metals (e.g. lead, mercury or arsenic) may occur due to an accidental accumulation of heavy metals when the medicinal plant grows on contaminated soil.[13] Medicinal plants may also be exposed to pesticides/herbicides during their growth and may have accumulated heavy metal components from these treatments.[14] Alternatively, plants growing in polluted air may also accumulate heavy metals. For example, plants growing near busy roads may accumulate lead from the traffic fumes, and this lead may reach levels that may be toxic.[15] Furthermore, harvested plant material and/or herbal medicines may become contaminated with heavy metals when stored incorrectly or when treated with chemical preservatives.[16] The levels of heavy metal contaminants is often not measured and reported for herbal medicine preparations.

Alternatively, contamination of herbal medicines with heavy metals may occur intentionally during the manufac-

ture of the herbal medication. Many traditional medicinal systems, including Traditional Chinese Medicine (TCM), Ayurveda (a traditional Indian medicinal system), as well as some African and South American medicinal systems, are known to intentionally include heavy metals in some herbal medicines. Ayuverdic preparations called Bhamas are known to contain heavy metals.[17] Similarly, heavy metals such as lead, silver and mercury have been reported in traditional medicines (Kushtas) from Pakistan.[18] Mercury compounds are often included in TCM preparations prescribed as tranquilisers and anticonvulsants and for the treatment of ulcers.[16] TCM physicians will also often include lead, cadmium or chromium in herbal medicines for the treatment of heart disease and stroke.[19]

A number of studies have sought to estimate the prevalence of heavy metal contamination (whether intentional or unintentional) in traditional herbal medicines. For example, one Indian study has reported that 64% of a selection of herbal remedies tested contained lead at potentially toxic concentrations.[16] Furthermore, approximately 95% of Ayuverdic medicines tested were found to contain mercury levels in excess of the legal limit (1 ppm).[20] This same study showed variability of mercury concentrations between similar remedies produced by different manufacturers, also highlighting the need for manufacturing standards. Many Chinese herbal medicines are also known to contain high levels of heavy metals. One study has reported high levels of copper, zinc, nickel, cobalt, manganese, chromium, molybdenum, iron, calcium, magnesium, cadmium and lead in multiple TCM preparations used to treat diabetes.[21] Extremely high levels of mercury and arsenic have also been reported is some traditional Chinese medicines.[22] Better quality and safety controls for the production of herbal medications exist in other Asian countries. These countries would be expected to have lower levels of heavy metals in their herbal medicines. For example, both Malaysia and Singapore have strict controls on heavy metal levels in their locally produced herbal preparations. Surveys of Malaysian[23] and Singaporean herbal medicines[24] detected only 8% and 2% of herbal medicine preparations respectively with levels of metals exceeding the safe level. Whilst this may still seem unacceptably high, it is much better than the other Asian regions surveyed and demonstrates that the safety/quality standards have begun to work in these countries.

High levels of lead,[25] arsenic and manganese[26] have also been reported in traditional African medicines. Lead has also been detected in folk remedies from Oman, the United Arab Emirates and Saudi Arabia, whilst mercury has also been reported in some preparations.[27-29] Similarly, cases of heavy metal poisoning also continue to be reported in Europe and North America. Several studies report high levels of mercury, arsenic and lead in herbal preparations in the UK.[30,31] However, it must be pointed out that these medicines were not produced in the UK, but instead were imported from India and China. Similarly, heavy metal poisoning from the use of Ayuverdic medicines has been reported in many other regions of the world including USA, Canada, Australia, Israel, Germany and the Netherlands.[32,33] Reports of heavy metal content in herbal medicines from other regions of the world are not as prevalent, although similar trends would be expected, especially in regions that import herbal medicines.

Contamination of Herbal Medicines with Allopathic Medicines

In contrast with heavy metal contaminants, contamination of herbal medicines with allopathic medicines is almost exclusively intentional. Allopathic medicines may be included in traditional medications to increase the speed of the herbal medicines response and/or to increase its effectiveness. Most countries now have strict regulatory systems which do not allow adulteration of herbal medicines with allopathic drugs. However, in many of the countries where herbal preparations are manufactured, it is considered acceptable practice to include allopathic medicines provided that the type and quantity of the drug is specified on the packaging. However, many manufacturers still fail to report the allopathic additives. A report of imported Asian medications in USA revealed that 257 herbal preparations (out of 260 tested) contained allopathic drugs.[34] of more concern, 17 of these products contained pharmaceuticals that were not declared on the labelling. A survey of Chinese medicines in Malaysia further illustrates this point. Malaysian regulation of herbal medicines is amongst the strictest in Asia. Despite this, a survey of herbal preparations in Chinese medicine shops found 83% of herbal arthritis medications contained phenylbutazone (an aspirin like anti-inflammatory drug). Presumably, these medicines were imported from China, where the adulteration regulations are not as rigorous.

Studies in other parts of Asia (particularly in countries with high Chinese populations) show that adulteration of herbal medicines with allopathic pharmaceuticals is common practice. A study of 65,748 Chinese medicines in Hong Kong[35] showed that a high proportion contained allopathic medicines. Of most concern was the presence of sidenafil, tadalafil, sibutramine and N-nitro fenfluramine in Chinese herbal preparations to treat obesity and

impotence. Similarly worrying was the levels of adulteration seen in Taiwanese medications. One survey of Taiwanese herbal medications reported that 26% of the medicines tested contained at least one adulterant, most commonly acetaminophen, indomethacin, hydrochlorothiazide, prednisolone, chloroxazone and ethoxybenzamide.[36] Many of these drugs may cause serious adverse side effects, resulting in life threatening disorders. A similar study by the Taiwanese FDA in 1992 reported that approximately 30% of the analgesic and antirheumatic herbal preparations tested contained many of the same drugs, as well as aminopyrine and phenylbutazone.[37] The presence of aminopyrine and phenylbutazone is of particular concern as these drugs are no longer prescribed in many countries due to concerns regarding their safe use. Furthermore, a study of Indian herbal medicines reported that 38% of the anti-asthma and anti-arthritis preparations tested were adulterated with steroids.[38]

Whilst adulteration of herbal medicines with allopathic drugs is particularly prevalent in Asian countries, it appears to be a widespread practice and has been reported in countries as diverse geographically and culturally as Australia, Belgium, Canada, The Netherlands, the UK and USA.[16] Often the compounds added to the herbal medications imported into Western countries are derivatives of restricted allopathic pharmaceuticals, in an attempt to bypass regulatory restrictions in these countries. An example of this is the addition of N-nitrosofenfluramine (instead of fenfluramine which is banned in several countries) to Asian herbal weight loss preparations. Whilst this practice has enabled the manufacturers/importers to bypass the restrictions in some countries, it is particularly concerning as N-nitroso compounds have been linked with hepatic carcinogenesis.[39] Numerous reports of hepatotoxicity in Japan have been linked to the use of imported herbal weight loss remedies containing N-nitrosofenfluramine.[40]

Complex combinations of herbal medicines and allopathic drugs have potential health implications for a number of reasons. Firstly, as already described for N-nitroso additives, the adulterant may itself be capable of producing adverse effects. Also, the allopathic constituent of the herbal medicine may actually exacerbate the disease state/condition for which the herbal medicine is being taken. Furthermore, the adulterant may oppose the effect of the herbal medicine, negating its usefulness. Alternatively, the allopathic adulterant may have a synergistic effect to the herbal medication which, in high enough doses may result in an overdose response. Harmful interactions may occur between the herbal medicine and the allopathic constituents. Finally, as herbal medicines are often taken as needed instead of as a prescribed dosage, there is potential that any added allopathic compounds may be taken in excess of its safe dosage or for an extended duration, resulting in the patient unknowingly exceeding the safe limits.

Contamination with Animal Products

Some herbal preparations may also contain animal parts/compounds. Some of these animal additives may themselves be potentially toxic. For example, some Chinese herbal medicines and aphrodisiacs contain toxins obtained from the skin glands of toads (especially *Bufo marinus* and *Bufo alvarius*) or from puffer fish (family Tetraodontidae).[41] These bufotoxins and tetrodatoxins have similar molecular structures and pharmacological effects to digoxin.[42] Thus, as with digoxin, the bufotoxin and tetrodatoxins may have desired effects at low concentrations but become potentially lethal at increased concentrations. Furthermore, patients also using digoxin at a prescribed dosage may still overdose when also using medicines containing bufotoxins or tetrodatoxins. This may result in nausea and vomiting, slowing of the heart rate and palpitations, insomnia and loss of balance/intoxication and in extreme cases, death.[43]

A further concern with herbal preparations containing animal products is the potential to spread infections. For example, nu bao, a Chinese herbal preparation containing ginseng, milk-vetch and Tang Kuei root, is used in TCM to maintain women's health by energising and maintaining hormone function. Nu bao preparations may also contain animal ingredients including deer antler and donkey skin.[44] These animal components are potential sources of bacteria and viruses and could therefore transmit infection. Of even more concern, some nu bao preparations may also contain human placenta.[44]

Plant Toxins

Some plants, including those used therapeutically, may be toxic to humans and may even be lethal at higher than therapeutic doses. The naturally occurring toxins in these plants are generally referred to as phytotoxins. An example of a phytotoxin with beneficial medicinal effects is the cardiac glycoside digoxin which is present in plants of the genus Digitalis, including foxglove (Digitalis purpurea). Digoxin is an antiarrhythmic agent which is used to control the heart rate, particularly in irregular or rapid arterial fibrillation. It is often prescribed in patients with congestive heart failure and is a very useful drug in therapeutic doses. It functions by inhibiting sodium-potassium ATPase, resulting in increased intracellular sodium ion concentrations and thus a decreased cross membrane gradient.[45] This in turn inhibits the cardiac sodium-cal-

cium exchanger, thereby resulting in increased cytosolic calcium concentrations. The increased calcium is stored in the sarcoplasmic reticulum. Upon cardiac contraction (action potential), more calcium is released from the sarcoplasmic reticulum resulting in a positive iontropic effect and increased contractility. Digoxin also effects the parasympathic nervous system and is also used to treat cardiac arrhythmias and to slow the ventricular rate during atrial fibrillation.[46] At higher doses, digoxin toxicity can result in nausea, vomiting, diarrhoea, abdominal pains, hallucinations, delirium and severe headaches. In severe toxicity, the individual may also suffer from bradycardia (an irregular and slow heart rate below 60 beats per minute), tremours and convulsions. In severe toxicity, digoxin may even even block cardiac contraction entirely and may be life threatening.[48]

It is evident from the example of digoxin that the concentration of toxic constituents in herbal preparations, and thus the dose that the patients receive, is an important consideration when using or prescribing herbal medications. The presence of a phytotoxin (such as digoxin) does not necessarily imply that adverse effects will always result from taking the preparation. Indeed, the digoxin example highlights the fact that phytotoxins can be useful medicinal agents. However, it is important to be aware of the concentration of any phytotoxins in a herbal preparation, the dosage of the preparation taken, and the duration the herbal preparation will be taken for. Herbal teas and medicinal honeys are examples of pharmacognostic preparations where the amount and/or frequency of consumption may be cause for caution as large quantities of the medication may often be consumed over long periods, potentially resulting in toxicity.[47,48] Furthermore, the preparation and method of usage of some herbal medications (such as teas) may result in increased concentrations of some phytotoxins, especially for the water soluble compounds.[47]

A number of classes of toxic constituents including pyrrolizidine alkaloids, glycosides, glycoalkaloids, saponins and psoralens may be present in plants and herbal medicines. Arguably the class of phytotoxin most frequently associated with toxicity in humans and animals is the pyrrolizidine alkaloids (PA).[49,50] Some PA's have been reported to be cytotoxic and therefore have potential as anticancer drugs.[50,51] Paradoxically, some PA's have also been shown to be carcinogenic.[49] Studies have shown that only unsaturated PA's, are convertible to cytotoxic pyrroles and are therefore the most likely class of PA to be toxic to humans.[50] Unsaturated PA's are converted in the liver to electrophyllic pyrroles that subsequently cause damage to the liver, and in some cases, also the lungs, kidney and heart.[50] Other PA's are known to affect genes and gene function (genotoxic).[51]

Comfrey, one of the most popular herbs in traditional European ethnopharmacology, is an example of a medicinal herb which contains toxic PA's.[52] It is traditionally used topically for injuries or joint pain and should not be used internally or on broken skin. Its PA components may cause occlusion of the small veins in the liver, resulting in cirrhosis and eventually liver failure. Individuals suffering from comfrey poisoning often present with an enlarged liver (heptomegaly) and abdominal pain. In Australia, the medicinal use of comfrey has been banned and it is listed as a dangerous poison.[53] Its usage for medicinal purposes has also been restricted in Canada and the USA.[54]

Furthermore, some plants may contain allergens. The traditional Asian medicine banha (derived from the root of *Pinellia ternata*) is used as an expectorant and cough suppressant. A recent study has reported on the induction of asthma by banha.[55] This study also determined that this induction of asthma was via an IgE mediated mechanism. In total, 7 *P. ternata* allergens capable of inducing IgE mediated bronchoconstriction in exposed patients were detected in this study. Asthma inducing allergens have also been detected in other herbal medicines including *Dioscorea batatas*[56] and ginseng.[57] Furthermore, numerous herbal medicines including Aloe vera, cumin, echinacea, garlic, kava and tea tree oil have been shown to be capable of inducing adverse allergic dermalatological reactions in some individuals. The incidence of allergic reactions will vary from individual to individual and may increase with long term usage/exposure.

Clinical effects of exposure of individuals with allergies to allergens generally occurs rapidly and may include symptoms ranging from minor annoyances (e.g. pruritus, rash, flushing and sneezing) to more serious, life threatening symptoms (e.g. decreased blood pressure, dangerous alterations in the heart rate and rhythm and severe breathing difficulties). Due to the unpredictability of severity of an allergic response and the potential life threatening consequences, it is best for individuals with known allergies to avoid exposure to allergen containing herbs.

Pesticide Contamination

Medicinal plants are often sprayed with pesticides and fertilisers during cultivation, prior to harvesting. Furthermore, plants may accumulate potentially dangerous chemicals from environmental pollution. Studies of

agricultural plants (including some plants used in herbal medicines) in Japan found residual agricultural chemicals in many herbs.[58,59] Disturbingly, the banned pesticide DDT was detected in some herbs used as medicines in these studies. Synthetic pyrethroids were also detected in a wide range of agricultural products (including medicinal herbs). Studies in Hong Kong have reported that all of the Chinese herbal medicines tested contained levels of pesticides such as quintozene and hexachlorobenzene that were of concern.[60] Similarly, a survey of cumin (a herb for used treating childhood coughs, aches and itching) from an Egyptian market found levels of the organophosphate insecticide profenofos at twice the limits permitted by the WHO.[61] This finding is concerning as cumin is often used in Egypt to treat ailments in children. The low body weight of children make them particularly vulnerable to toxic chemicals.

DRUG-DRUG INTERACTIONS

Research into the reactions between herbal medicines and other drugs (either other herbal medicines and/or allopathic medications) is not as advanced as for pharmaceutical drugs. Descriptions of herb-drug interactions are often imprecise and nonspecific. Furthermore, many of the studies that do exist are anecdotal and poorly documented. Drug-drug interactions may either affect the metabolism of one or both of the drugs, thus altering their bioavailability, resulting in a wide variety of clinical affects (Table 2). An understanding of drug-drug interactions is particularly important when serious and/or life threatening diseases are being treated. Interactions of clinical relevance include:

- Oral anticoagulant drugs
- Oral hypoglycaemic drugs
- Antibiotics
- Antiepileptic drugs
- Anti-arrhythmic drugs
- Oral contraceptives
- Antiretroviral drugs

Pharmacokinetic Interactions

Herb-drug interactions which disrupt the absorption, distribution, metabolism and excretion of a drug are considered to be pharmacokinetic interactions (Table 2). Ingested agents may alter the absorption of other drugs from the gastrointestinal tract (GIT). In other cases, the metabolism, distribution and/or excretion of a compound may be affected. The clinical importance arises when the pharmacokinetic properties (such as Tmax, Cmax or AUC) of these agents is modified through drug-herb interactions,[62] such that drug efficacy and ultimate toxicity is subsequently affected. This occurs more frequently for drugs possessing narrow therapeutic windows, such as digoxin.[63]

Interactions Affecting drug absorption

The mechanisms of action by which pharmacokinetic drug-herb interactions occur vary widely. Drug absorption can encompass one or more different phases which contain different mechanisms of action. Drugs may affect the upper GIT by altering gastric pH and motility,[64] which impact drug solubility and release.[65] A recent study reported that the Chinese herbal preparations Si-Jun-Zi-Tang (SJZT) and Shen-Ling-Bai-Zhu-San (SLBZS) significantly neutralized gastric acid.[66] The Cecropia glazioui Sneth (Cecropiaceae) plant extract, a popular Latin American folk medicine, was found to reduce stomach acidity by inhibiting gastric proton pumps in animal studies.[67] Such treatments could affect other, co-administered prodrugs which require a low stomach pH for activation.

Various human and animal model studies indicate that stomach motility can be stimulated by capsaicin (from the chilli pepper Capsicum annuum),[68] as well as Vernonia amygdalina leaf extracts,[69] the mixed-extract herbal formulation known as Iberogast (also known as STW 5) which includes components such as Citrus limonum, Glycyrrhiza glabra, Mentha piperita and Matricaria recutita,[70] and ginger (Zingiber officinale) extracts,[71] while diarrhoea can be caused by Cassia angustifolia (senna) extract.[72] Furthermore, a common use for Aloe vera is as a laxative.[73] The ramifications of using these drugs are reduced gastrointestinal transit times for any co-administered drugs, and thus a lowered absorption.

Co-administered compounds may interact within the GIT to form insoluble chemical complexes, which reduces the bioavailability of both agents.[74] Chilli powder (Capsicum annuum) has been found to lower iron absorption in the GIT in humans[75] and the polyphenolic compounds in the spice (capsaicin) presumably causes this by forming complexes with iron within the gut.[76] The high mineral content of dandelion (Taraxacum officinale) is believed to result in the formation of complexes between drugs, resulting in a decreased absorption.[76] Another study showed that the major polyphenol constituent of green tea formed an insoluble precipitate following interaction with an anticancer drug, sunitinib, in the stomach,[77] thereby decreasing sunitinib absorption.

Table 2: Known herb-drug interactions (both pharmokinetic and pharmacodynamic).

Herbal Medicine	Species Name	Allopathic Drug	Mechanistic Basis	Clinical Effect	Ref.
Adonis	Adonis vernalis	Digoxin	additive effect of constituent cardiac glycosides	increase in adverse effects of digoxin	152
		Quinidine	additive effect of constituent cardiac glycosides	increase in adverse of quinidine	
Aloe	various Aloe species including *Aloe ferox Aloe barbadensis,*	cardiac glycosides (e.g. digoxin)	decreases blood potassium levels, can cause diarrhoea and decrease drug absorption	increases the toxicity of cardiac glycosides	12, 73, 111, 143, 144, 152
		Diuretics	increases potassium loss from the gut	lower body potassium levels may cause lethargy and muscle weakness	
		Tolbutamide	prolongs the presence of drug in the blood	hypoglycaemia	
		Warfarin	unknown	increases the effect and toxicity of warfarin	
Arnica	Arnica montana	Warfarin	arnica coumarin compounds may increase bleeding	may cause bleeding	131, 132, 152
Ashwagandha	Withania somnifera	barbituates and benzodiazepines	unknown	enhances sedative effect	152
Astralagul	Astragalus propinquus	immunosuppressants	reduces immunosuppressant activity	possibility of tissue graft rejection	152
Avocado	Persea americana	Warfarin	reduces absorption and may also increase metabolism	decreased anticoagulant activity	152
Baizhi	Angelica dahurica	Tolbutamide	inhibits cytochrome P450 2E1 isozyme and thus increases the drugs half life	hypoglycaemia	152
		benzodiazepines	reduces metabolism and increases the drugs half life	increases the effects (e.g. drowsiness)	
		insulin	unknown	hypoglycaemia	
Betel nut	Piper betle	Flupentixol	unknown	bradykinesia, rigidity	107, 108, 152
		Fluphenazine	unknown	tremor, stiffness	
		Prednisolone	bronchoconstriction	loss of control of asthma	
		Salbutamol	bronchoconstriction	loss of control of asthma	
		Procyclidine	antagonistic effect on the anticholinergic activity of betel nut	bradykinesia, rigidity	
		Beta blockers, calcium channel blockers digoxin	unknown	causes bradycardia	
Bilberry leaf	Vaccinium spp.	Warfarin	decreases platelet aggregation	increases bleeding	152
		Aspirin	decreases platelet aggregation	increases bleeding	
Bitter melon	*Momordica charantia*	Chlorpropamide	bitter melon decreases glucose loss in the urine	may interfer with blood glucose control	112, 152

Black pepper	Piper *nigrum*	phenytoin	Inhibits cytochromes P450 3A4 and 2C9	prolongs the presence of the drug	97, 98, 152
		Propranolol	Inhibits cytochromes P450 1A1 and 1A2	prolongs the presence of the drug	
		Rifampicin	Inhibition of P-gp transport proteins	prolongs the presence of the drug	
		Theophylline	inhibition of several cytochromes P450	prolongs the presence of the drug	
Black cohosh	*Actaea racemosa*	aspirin	contains coumarin compounds may increase bleeding	may cause bleeding	124, 152
		Cisplatin	unknown	decreased effectiveness of this anticancer drug	
		Clopidogrel	contains coumarin compounds may increase bleeding	may cause bleeding	
		Dipyridamole	contains coumarin compounds may increase bleeding	may cause bleeding	
		Docetaxel	unknown	increases the cytotoxic effect of docetaxel	
		Doxorubicin	unknown	increases the cytotoxic effect of docetaxel	
		Heparin, ticlopidine, warfarin	contains coumarin compounds may increase bleeding	may cause bleeding	
		Anaesthetics, antihypertensives	unknown	increases hypotensive effects of anaesthetics. Risk of low blood pressure	
Boldo	*Peumus boldus*	Warfarin	has anticoagulant properties	increased risk of bleeding	152
Broom	*Cytisus scoparius*	Digoxin	unknown	increase in adverse effects of digoxin	111, 152
		Beta blockers (e.g. propranolol)	unknown	increases the effects of beta blockers	
		Tricyclic antidepressants	unknown	may cause cardiac arrhythmias	
Caffeine	various plant species including *Coffee arabica* and *Camelia*	Clozapine	unknown	elevated blood levels of the drug	152
	sinensis	Lithium	unknown	elevated blood levels of the drug	
		Theophylline	unknown	elevated blood levels of the drug	
Capsicum spp.	Capsicum spp.	ACE inhibitors	depletes substance P	increases cough	68, 75, 76, 111, 121, 152
		Theophylline	increases absorption and bioavailability of drug	increased risk of toxicity	
Catnip	*Nepeta cataria*	barbituates and benzodiazepines	may increase sedative effect	increased CNS depression	111, 121, 152
Chamomile	*Matricaria recutita*	Aspirin	contains coumarin compounds may increase bleeding	increased risk of bleeding	111, 124, 152

		Clopidogrel	contains coumarin compounds may increase bleeding	increased risk of bleeding	
		Dipyridamole	contains coumarin compounds may increase bleeding	increased risk of bleeding	
		Heparin	contains coumarin compounds may increase bleeding	increased risk of bleeding	
		Ticlopidine	contains coumarin compounds may increase bleeding	increased risk of bleeding	
		Warfarin	contains coumarin compounds may increase bleeding	increased risk of bleeding	
Chaste tree	*Vitex agnus-castus*	Metoclopramide	contains constituents that are dopamine agonists	decreases the effect of dopamine antagonists	145, 152
Chinese wolfberry	*Lycium barbarum*	Warfarin	inhibits cytochrome P450 enzyme systems	Increased blood levels of warfarin, increased bleeding	98, 152
Condurango	*Marsdenia condurango*	Carbamazepine, paroxetine, ritonavir, sertraline	contains 7-hydroxy coumarin which is metabolised by cytochrome P450 2A6	may produce result in unpredictable drug levels in the blood	152
Cowslip	*Primula officinalis*	Antihypertensives	Has hypertensive effects	increased risk of high blood pressure	152
Curcurbita	Curcurbita spp.	Warfarin	unknown	increased anticoagulant effect of warfarin	152
Dandelion	*Taraxacum officinale*	Diuretics Antidiabetic drugs, antihypertensives, quinolone antibiotics (e.g. ciprofloxacin, nalidixic acid)	dandelion contains diuretic constituents dandelion contains a high mineral content which decreases drug absorption	may potentiate the diuretic effect blocks drud effects, resulting in effects including, high blood glucose levels, increased blood pressure etc.	76, 152
Dang gui	*Angelica sinensis*	Warfarin	may inhibit cytochromes P450 3A4 and 1A. Also contains coumarins which may increase bleeding	prolongs the time for clot formation during bleeding	111, 124, 152
Danshen	*Salvia miltiorrhiza*	Warfarin	additive anticoagulant effects	increased risk of bleeding	79, 152
Devil's claw	*Acacia senegal, Acacia* greggii	Digoxin	devil's claw contains cardioactive compounds	enhances the effect of digoxin, increases adverse effects	101, 111, 152
Echinacea	*Echinacea purpurea*	Anabolic steroids (e.g. methotrexate, amiodarone)	unknown	increases drug hepatotoxicity	126, 127, 152
		Azathioprine	unknown	decreases the drugs immunosuppressant effect increased risk og graft rejection	
		Corticosteroids	unknown	decreases the drugs immunosuppressant effect increased risk og graft rejection	
		Cyclosporin	unknown	decreases the drugs immunosuppressant effect increased risk og graft rejection	
		Tacrolimus	unknown	decreases the drugs immunosuppressant effect increased risk og graft rejection	
Elder	*Sambucus nigra*	Diuretics	elder contains diuretic constituents	may potentiate the diuretic effect	152

Ephedra	*Ephedra sinica*	Antihypertensives	opposing bioactivities,	increases blood pressure	103, 111, 124, 152
		Beta blockers	opposing bioactivities,	increases blood pressure	
		Decongestants	additive effects	increased heart rate, palpitations, sedation	
		MAO inhibitors	increased ephedrine levels as MAO inhibitors block ephedrine metabolism	hypertension	
		Stimulants (including caffeine and guarana)	additive effects, increasedheart rate, palpitations	additive stimulation, hypertension and increased heart rate	
Evening primrose	*Oenothera biennis*	Anticonvulsants (e.g. barbituates, phenytoin)	lowers the seizure threshold	increased tendency for seizure	125, 152
		Fluphenazine	lowers the seizure threshold	increased tendency for seizure	
Fenugreek	*Trigonella foenum-graecum*	Warfarin	contains coumarin compounds may increase bleeding	increased risk of bleeding	111, 121, 152
Feverfew	*Tanacetum parthenium*	Warfarin	contains coumarin compounds may increase bleeding	increased risk of bleeding	111, 124, 125, 152
Frangula	*Rhamnus frangula*	Multiple drugs	has laxative action which results in decreased drug absorption	decreases the efficacy of drugs	152
Garlic	*Allium sativum*	Chlorpropamide	unknown	decreases blood sugar levels resulting in hypoglycaemia	104, 111, 124, 125, 152
		Ritonavir	additive gastrointestinal effects	increased gastrointestinal symptoms	
		Saquinavir	induces cytochrome P450 3A4 enzyme	decreased blood levels of the drug resulting in a decreased effect	
		Warfarin	inhibition of platelet aggregation	prolongs the time for clot formation during bleeding	
Ginger	*Zingiber officinale*	Cardiac glycosides	ginger contains cardioactive constituents	potentiates the effect of other cardiac glycoside drugs	71, 104, 111, 124, 152
		Phenprocoumon	inhibits platelet aggregation	prolongs the time for clot formation during bleeding	
		Saquinavir	decreases blood levels of saquinavir	decreased activity of saquinavir	
		Warfarin	inhibition of platelet aggregation	prolongs the time for clot formation during bleeding	

Ginkgo biloba	*Ginkgo biloba*	Aspirin	increases the antiplatelet effect. Ginkgo biloba is a potent inhibitor of platelet activating factor (PAF)	enhanced bleeding	111, 124, 152
		Azprazolam	decreases blood levels of azprazolam	decreased activity of azprazolam	
		Digoxin	increased blood levels of digoxin	potentiates the effects of digoxin	
		Diltiazem	inhibits cytochrome P450 3A4	increased blood levels of diltiazem result in decreased blood pressure	
		Haloperidol	ginkgo biloba may scavenge free radicals produced by haloperidol treatment	increased effectiveness of the drug	
		Ibuprofen	increases the antiplatelet aggregatory activity	enhanced bleeding	
		Trazodone	unknown	increased sedative effect	
		Nicardipine	Induction of cytochrome P450 3A2	loss of blood pressure control	
		Nifedipine	inhibition of cytochrome P450 3A4	elevated blood levels of nifedipine and increased risk of adverse effects	
		Omeprazole	Induction of cytochrome P450 2C19	reduced efficacy of omeprazole	
		Thiazide diuretics	unknown	increased blood pressure	
		Ticlopidine	unknown	increased bleeding	
		Tolbutamide	increased metabolism of tolbutamide	Loss of control of blood sugar levels	
		Valproate	unknown	increased risk of seizures	
		Warfarin	synergistic anticoagulant effects	enhanced bleeding	
		Trazodone	increased GABA activity in the brain; may induce cytochrome P450 3A4 resulting in the formation of active metabolites	increases the sedative effect and may result in coma	
Ginseng	*Panax ginseng*	Bumetanide	unknown	decreases the diuretic effect	111, 121, 124, 152
		Ethacrynic acid	unknown	decreases the diuretic effect	
		Furosemide	unknown	decreases the diuretic effect	
		Isocarboxazid	unknown	induces manic symptoms, headache, insomnia, tremors	
		Nifedipine	inhibition of cytochrome P450 3A4	elevated blood levels of nifedipine and increased risk of adverse effects	
		Estrogens, corticosteroids	additive effects	increased effects of these drugs	
		Phenelzine	similar, additive effects	induces manic symptoms, headache, insomnia, tremors	
		Torasemide	unknown	decreases the diuretic effect	
		Tranylcypromine	unknown	induces manic symptoms,	
		Warfarin	antiplatelet action, induction of cytochrome P450 enzymes	headache, insomnia,tremors	
				increases the effect of warfarin, increased bleeding	
		Antidiabetic agents	ginseng constituents have hypoglycaemic activity	hypoglycaemia	

Goldenseal	*Hydrastis canadensis*	Aspirin	unknown	decreases the antiplatelet effect of aspirin	111, 124, 152
		Clopidogerol	unknown	decreases the antiplatelet effect	
		Dipyridamole	unknown	decreases the antiplatelet effect	
		Fexofenidine	inhibits cytochrome P450 3A4	elevated blood levels of fexofenidine and increased risk of adverse effects	
		Heparin	unknown	decreases the anticoagulant effect	
		Ticlopidine	unknown	decreases the antiplatelet effect	
Grapefruit	*Citrus paradisi*	Amiodarone	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	93-96, 152
		Amlodipine	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Atorvastatin	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Benzodiazepines	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Buspirone	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Carbamazepine	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Cisapride	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Clomipramine	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Cyclosporin	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Digoxin	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Erythromycin	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Ethinylestradiol	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Fluvoxamine	effects activity of cytochrome P450 enzymes	elevated amiodarone levels and enhanced effect of the drug	
		Indinavir	effects activity of cytochrome P450 enzymes	delayed onset of the drugs effect	
		Losartan	effects activity of cytochrome P450 enzymes	unpredictable blood levels of losartan, may result in poor control of blood pressure	
		Lovastatin	effects activity of cytochrome P450 enzymes	unpredictable blood levels of lovastatin, may increase effects of the drug	
		Nicardipine	effects activity of cytochrome P450 enzymes	elevated blood levels of nicardipine, may result in low blood pressure	
		Nisoldipine	effects activity of cytochrome P450 enzymes	elevated blood levels of drug may result in low blood pressure	
		Praziquantel	effects activity of cytochrome P450 enzymes	elevated blood levels of drug may result in increased side effects	
		Quinidine	effects activity of cytochrome P450 enzymes	delayed onset of the drugs therapeutic effects	
		Simvastatin	effects activity of cytochrome P450 enzymes	elevated blood levels of drug may result in increased side effects	
		Sildenafil	effects activity of cytochrome P450 enzymes	elevated blood levels ofdrug may result in increased side effects	
		Verapamil	effects activity of cytochrome P450 enzymes	elevated blood levels of drug may result in increased side effects	

Green tea	*Camellia sinensis*	Clozapine	may induce cytochrome P450 1A2	decreased effectiveness of the drug	77, 99, 152
		Theophylline	additive effect due to the caffeine in the tea	increased stimulation, palpitations and increased heart rate	
		Warfarin	vitamin K in green tea may antagonise warfarin	decreased anticoagulation and increased risk of thrombosis	
Guar gum	Cyamopsis spp.	Digoxin	decreases absorption of the drug	reduced blood levels of the drug, producing low response	152
		Metformin	decreases absorption of the drug	reduced blood levels of the drug resulting in poor control of diabetes	
		Bumetanide	decreases absorption of the drug	reduced blood levels of the drug, producing low response	
		Penicillin antibiotics	decreases absorption of the drug	reduced blood levels of the drug, producing low response	
		Glibenclamide	decreases absorption of the drug	reduced blood levels of the drug resulting in poor control of diabetes	
Guarana	*Paullinia cupana*	Theophylline	additive effect	increased stimulation, palpitations and increased heart rate	99, 152
Hawthorn	Crataegus spp.	Cardiac glycosides	hawthorn constituents	potentiates the effects of	152
		(including digoxin)	stimulate heart muscle and cardio control centres	cardiac glycosides	
		Antihypertensives	unknown	enhances antihypertensive effect resulting in hypotension	
		Nitrates	unknown	enhances antihypertensive effect resulting in hypotension	
Hops	*Humulus lupulus*	Hypnotics	additive sedative effects	potentiates the effects of hypnotics	111, 152
		Phenothiazine type antipsychotics	unknown	hyperthermia	
Horse chestnut	*Aesculus hippocastanum*	Aspirin	contains coumarin compounds may increase bleeding	increased risk of bleeding	152
		Warfarin	contains coumarin compounds may increase bleeding	increased risk of bleeding	
Huang qin	*Scutellaria baicalensis*	Irinotecan	unknown	lessens the toxic effects of some anticancer drugs in the gut	152
African potato	*Hypoxis hemerocallidea*	All drugs which are metabolised by cytochrome P450 3A4	inhibition of cytochrome P450 3A4	the blood concentrations of a wide range of drugs, and thus the risk of side effects, is increased	152
Ispaghula	several Psyllium spp.	Many drugs	ispaghula has a laxative effect and may decrease the absorption of many drugs	reduced blood levels and thus reduced effectiveness of many drugs	70, 152
Kava kava	*Piper methysticum*	Acetamionphen	unknown	increases the incidence of liver and kidney damage	84, 97, 124, 152
		Barbituates and benzodiazepines	Compounds in kava kava bind GABA receptors (the same receptors that benzodiazepines bind)	additive/synergistic effects resulting in increased sedation and sometimes coma	
		Haloperidol	unknown	increased side effects of haloperidol	
		Risperidone	unknown	increased side effects of	
		Metoclopramide	unknown	increased side effects of	
		Levodopa	antagonistic effects	reduced efficacy of levodopa	
Kelp (Fucus)	Fucus spp.	Thyroxine	kelp contains iodine which has roles in thyroid hormones	interferes with thyroid replacement	152

Khat	Catha edulis	Penicillin, ampicillin, amoxacillin	may reduce absorption due the formation of antibiotic-tannin complex	reduced blood antibiotic levels	83, 152
Kudzu	Pueraria lobata	Verapamil	additive effect on calcium channels	additive hypotenstive effects	125, 142, 152
		Triptans (e.g. Sumitriptan)	additive effects on neurotransmitters	increased adverse side effects	
		Methotrexate	reduced metabolism resulting in higher blood drug levels	increased risk of toxicity	
Lavender	Lavandula spp.	Barbituates and benzodiazepines	additive effects	increased sedative effect	152
		Chloral hydrate	additive effects	increased sedative effect	
Liquorice	*Glycyrrhiza glabra*	Digoxin	lowers blood potassium levels	increased sensitivity to digoxin	111, 124, 152
		Ethinylestradiol	ethinylestradiol may increase sensitivity to glycyrrhizin acid constituent of liquorice	hypertension, edema and other adverse side effects	
		Prednisolone	glycyrrhizin blocks clearance of prednisolone from the blood thus increasing the concentration	may increase prednisolone side effects	
		Spironolactone	unknown	reduces diuretic effect of spironolactone	
		Loratidine, quinidine, procainamide	unknown	Multiple ECG effects increased side effects	
Milk thistle	Silybum spp.	Amiodarone	may inhibit cytochrome P450 3A4	enhanced antiarrhythmia activity	152
		Indinavir	unknown	reduces indinavir levels and thus efficacy	
Neem	*Azadirachta indica*	Azathioprine	unknown	decreases the immunosuppressine effect	104, 111, 152
		Imuran	unknown	decreases the immunosuppressine effect	
		Glimepiride	additive effect in lowering blood glucose levels	may cause hypoglycaemia	
		Glucotrol	additive effect in lowering blood glucose levels	may cause hypoglycaemia	
		Micronase	additive effect in lowering blood glucose levels	may cause hypoglycaemia	
		Orinase	additive effect in lowering blood glucose levels	may cause hypoglycaemia	
		Prednisolone	unknown	decreases the immunosuppressine effect	
		Tolinase	additive effect in lowering blood glucose levels	may cause hypoglycaemia	
		Zenapax	unknown	decreases the immunosuppressine effect	
Nettle	*Urtica dioica*	Various diuretic drugs	nettle constituents have additive diuretic effect	increases diuretic activity	111, 152
Oleander	*Nerium oleander*	Digoxin	additive effects	increased risk of cardiac toxicity	111, 118, 152
Papaya	*Carica papaya*	Warfarin	unknown	increases the anticoagulant effect of warfarin	152
Passion flower	Passiflora incarnata	Hypnotics	passion flower contains constituents with sedative effects	increases the effects of hypnotic drugs	111, 152

Psyllium	*Plantago ovata*	Lithium	decreases blood lithium concentrations	decreases the effect of lithium treatment	152
Rhubarb	*Rheum officinale*	Cardiac glycosides (e.g. digoxin)	lowers blood potassium levels, causes diarrhoea which decreases drug absorbtion	increased sensitivity to cardiac glycosides	111, 152
		Diuretics	lowers blood potassium levels by causing loss from the gut	low potassium, lethargy, muscular weakness	
Rosemary	*Rosmarinus officinalis*	Antidiabetic agents	hyperglycaemia	antagonises the blood glucose lowering effects of antidiabetes drugs	111, 152
Saw palmetto	*Serenoa serrulata*	Finasteride, flutamide	inhibition of 5α reductase, inhibition of dihhdrotestosterone binding to receptors	affects all levels of male hormone (androgen) effect	85, 111, 152
		Oral contraceptives, hormone replacement therapy	unknown	affects estrogens functions	
		Disulfiram	unknown	nausea, vomitting	
		Warfarin	unknown	increased anticoagulant effect	
		Ibuprofen	inhibition of cyclooxygenase, and 5-lipoxygenase	risk of serious bleeding	
		Naproxen	inhibition of cyclooxygenase, and 5-lipoxygenase	risk of serious bleeding	
		Metronidazole	unknown	nausea, vomitting	
Scopolia	Scopolia carniolica	Tricyclic antidepressants	unknown	increased effectiveness of tricyclic antidepressants	152
		Amantadine	unknown	increased effectiveness of amantadine	
		Quinidine	unknown	increased effectiveness of quinidine	
Sea buckthorn	Hippophae spp.	Cyclophosphamide	unknown	decreases the cytotoxic effect of the drug thus reducing its effect	152
		Farmorubicin	unknown	decreases the cytotoxic effect of the drug thus reducing its effect	
Senna	Senna spp.	Multiple drugs	Decreases the absorption of many drugs due to its laxative effect	reduced blood levels of the drug, producing low response	52, 72, 111, 152
Soy/Soya	Glycine max	Warfarin	induces several cytochromes P450 including 3A isozymes	decreased anticoagulant effects of warfarin	152
		Tamoxifen	phyto-estrogens in soy may counteract the drugs effects	may reduce drug levels of tamoxifen resulting in a poor response	
Squill	Scilla spp.	Quinidine	Cardioactive glycosides increase force of cardiac contraction and slows the contraction rate	increased effectiveness and risk of adverse effects including arrhythmias	148, 152
		Digoxin	Cardioactive glycosidesincrease force of cardiac contraction and slows the contraction rate	increased effectiveness and risk of adverse effects	
		Sympathomimetics (e.g.adrenaline, isoprenaline)	unknown	increased risk of arrhythmias	
		Methylxanthines	unknown	increased risk of arrhythmias	
		Phosphodiesterase inhibitors	unknown	increased risk of arrhythmias	

St John's wort	Hypericum perforatum	Amityptyline	Induction of cytochrome P450 3A4	decreased drug levels and thus decreased effectiveness	87-92, 124, 152
		Anaesthetic drugs	unknown	delayed onset of anaesthesia	
		Anti-HIV drugs (e.g. indinavir, lamivudine, amprenavir)	Induction of cytochrome P450 3A4	decreased drug levels and thus decreased effectiveness	
		Anticonvulsants (e.g. phenytoin, phenobarbitol)	Induction of cytochrome P450 3A4	decreased drug levels and thus decreased	
		Benzodiazepams	Induction of cytochrome P450 3A4	effectiveness decreased drug levels and thus decreased effectiveness	
		Buspirone	Synergistic effects on 5-hydroxytryptamine receptors	hypomania	
		Cyclosporin	decreased bioavailability of the drug due to decreased intestinal absorbtion and Induction of cytochrome P450 3A4	risk of transplant rejection due to low cyclosporin levels	
		Digoxin	Decreased blood levels of digoxin	decreased digoxin effectiveness	
		Fenoxfenadine	Induction of cytochrome P450 3A4	low blood drug levels resulting in decreased antihistamine activity	
		Irinotecan	unknown	low blood drug levels resulting in decreased therapeutic effect	
		Loperamide	Cytochrome P450 induction	increased risk of serotonin syndrome	
		Methadone	Cytochrome P450 induction	Reduced blood methadone levels which may result in drug withdrawl	
		Midazolam	Cytochrome P450 induction	decreased drug levels and thus decreased effectiveness	
		Nifedipine	Induction of cytochrome P450 3A4	decreased effectiveness in lowering the blood pressure	
		Oral contraceptives	Cytochrome P450 induction	intermenstral bleeding, contraceptive failure	
		Serotonin reuptake inhibitors	Inhibits uptake of serotonin thus increasing serotonin effects	increases serotonin's sedative effects	
		Phenprocoumon	Cytochrome P450 induction	decreased anticoagulant effect	
		Quazepam	Induction of cytochrome P450 3A4	decreased drug levels and thus decreased effectiveness	
		Simvastatin	Induction of cytochrome P450 3A4	decreased drug levels and poor cholesterol lowering effect	
		Tacrolimus	Induction of cytochrome P450 3A4	decreased drug levels and increased risk of transplant rejection	
		Theophylline	Induction of cytochrome P450 1A2	decreased drug levels and increased risk of therapeutic failure	
		Verapamil	Induction of cytochrome P450 3A4	decreased effectiveness of verapamil	
		Warfarin	Induction of cytochrome P450 2C9	decreased blood warfarin levels and thus decreased anticoagulant effect	
Tamarind	*Tamarindus indica*	Aspirin	increases the bioavailibility of aspirin	may increase the adverse effects of aspirin	152
Valerian	*Valeriana officinalis*	Benzodiazepams	increases the concentration of GABA in the brain	increases the drugs sedative effects	111, 124, 152

Willow	Salix spp.	Anticoagulants	salicylate constituents in willow enhance the anticoagulant effect	increased bleeding	100, 152
		NSAIDS (e.g. Ibuprofen)	unknown, possibly a additive effect of salicylic acid and the NSAID	may increase gastro-intestinal ulceration and bleeding	
		Phenytoin	salicylate constituents compete with phenytoin for protein binding sites	increased blood levels of phenytoin	
Yohimbine	*Pausinystalia yohimbe*	Tricyclic antidepressants	increased stimulation of sympathetic nervous system	increases blood pressure	117, 152
		Tetracyclines	chelation of herbal constituents with antibiotic	may result in a poor response to tetracycline	
		Venlafaxine	unknown	Manic reactions	

Other drug absorption interactions can involve drug efflux transporters which line the GIT epithelial membranes[78] and play a detoxification role by expelling xenobiotic molecules from the enterocytes, thereby lowering systemic concentrations.[79] These comprise the ATP binding cassette (ABC) transporters such as P-glycoprotein (P-gp)[80] and multi-drug resistance-associated protein 2 (MRP-2).[81] However, the GIT enterocytes also contain influx transporters (or carrier uptake proteins) such as peptide transporter 1 (PepT1), organic-anion transporting polypeptides (OATPs) and monocarboxylate transporters (MCT1) which facilitate the absorption of drugs as well as many endogenous compounds.[82] Khat (Catha edulis) tannins may form complexes with some antibiotics, reducing their absorbance.[83] This reduces the blood antibiotic concentration and thus its efficacy.

Interactions affecting protein binding

Once an ingested drug is absorbed from the GIT into the bloodstream, a portion may bind to blood proteins, blocking the ability of the drug to pass into peripheral tissues. This effectively blocks/decreases the therapeutic activity of the drug as there is a lower effective concentration in the bloodstream. When another drug which can form a stronger bond with the same proteins is taken concurrently, the first drug may be displaced, effectively increasing the concentration of accessible drug. In some cases this may be beneficial, providing an enhanced therapeutic effect. However, it is likely to also increase the side effects and toxicity of the drug.

Herbal medicines and other drugs may also compete for binding to receptor proteins. Piper methysticum (kava kava) binds to the same GABA receptors as barbituates, resulting in additive/synergistic effects.[84] Thus, patients prescribed barbiturate sedatives who use kava kava concurrently will experience vastly increased sedation and in extreme cases this may result in coma. Similarly, Serenoa serrulata (saw palmetto) competes with dihydrotestosterone for binding to receptors.[85] This competitive inhibition of dihydrotestosterone function affects all levels of the hormones action. As dihydrotestosterone function is particularly important during male development, saw palmetto intake should be avoided during childhood and adolescence. Similarly, pregnant women should avoid saw palmetto usage as it may impact on fetal development.

Interactions affecting metabolism

Cytochromes P450 (CYPs) are the major enzymes involved in drug metabolism.[86] Medicine usage (both herbal and allopathic) may increase or decrease the activity of CYPs, affecting the metabolism of other drugs and endogenous hormones. This accounts for a major category of adverse drug interactions as changes in CYP enzyme activity may affect the metabolism and clearance of multiple drugs resulting in drug accumulation to toxic levels, or conversely, in increased clearance and thus decreased drug efficacy.

Hypericum perforatum (St John's wort) induces the production of cytochrome CYP 3A4.[87] This enzyme has a particularly broad substrate specificity, resulting in significant effects on the metabolism of numerous drugs. Notably, anti-HIV retroviral drugs such as indinavir, lamivudine and amprenavir are metabolised by CYP 3A4.[88] Thus taking these drugs concurrently with St John's wort induces rapid metabolism and clearance of these drugs, decreasing their efficacy. As anti-HIV retroviral drugs function to decrease the viral blood load, this may have profound detrimental effects, hastening the patients disease progression and increasing their ability to infect others.

Benzodiazepam drugs are also metabolised by CYP 3A4. The co-usage of St John's wort with benzodiazepam sedatives decreases the levels of benzodiazepams, resulting

in decreased effectiveness.[89] Concurrent use of St John's wort with ethylene estradiol containing oral contraceptives or nifedipine stimulates drug metabolism, resulting in contraceptive failure and decreased effectiveness in lowering blood pressure respectively.[90,91] of particular importance, organ transplant patients should avoid the use of St John's wort as it stimulates cyclosporine metabolism and thus increases the chances of tissue rejection.[92]

Citrus paradisi (grapefruit) ingestion also affects the metabolism of a wide variety of drugs. However, in contrast to St John's wort, grapefruit inhibits the activity of several CYP isoenzymes.[93] These decreased metabolic rates result in higher concentrations of drug persisting in the bloodstream for a longer time. For benzodiazepam drugs, this results in an increased sedative effect and greater chances of coma.[94,95] Similarly, cyclosporine, ethylene estradiol and numerous other drugs may persist in the patient's bloodstream significantly longer in patients ingesting grapefruit, increasing the risks of detrimental effects.[96]

Piper nigrum (black pepper) inhibits multiple CYP isoenzymes resulting in numerous pharmokinetic interactions. It inhibits CYP 3A4 and CYP 2C9, prolonging the presence of phenytoin in the blood. It also inhibits CYP 1A1 and 1A2 prolonging the effects of drugs such as propranolol which are metabolised by these enzymes.[97] Similarly, Lycium barbarum (Chinese wolfberry) inhibits enzymes involved in warfarin metabolism.[98] As warfarin is prescribed as a blood anti-coagulant in patients with some cardiac conditions, this is a particularly serious problem and Chinese wolfberry should be avoided by patients using warfarin.

Interactions affecting excretion

Drugs which alter the pH of the urine or alter the concentrations of specific ions necessary for renal interchange will interfere with the excretion of some drugs. Such an affect may decrease the excretion rate of a drug, increasing the patient's exposure and thus increase the possibility of toxicity and/or unwanted side effects. Alternatively, drugs which speed the rate of excretion will decrease the half-life of the drug in the bloodstream, thus lessening its therapeutic effects. Similarly, the rate of drug excretion is affected if two drugs taken concurrently use a common excretory mechanism. If one of the drugs is preferentially excreted, excretion of the other drug will be slowed and it may accumulate, increasing the possibility of toxicity. Furthermore, some drugs may inhibit specific renal enzymes required for the excretion of other drugs, resulting in similar toxicities.

Pharmacodynamic Interactions

Herb-drug interactions which elicit changes in the pharmacological effects of either drug are classed as pharmacodynamics interactions. Herbal medicines may have additive, synergistic or antagonistic effects when taken with other drugs. Paullina cupana (guarana) functions similarly to theophylline (both are stimulants). Taking both drugs concurrently results in increased stimulation, increased heart rate and palpitations.[99] Willow (Salix spp.) have additive effects with nonsteroidal anti-inflammatory drugs (NSAIDs), which may result in gastrointestinal ulceration and internal bleeding.[100] Devils claw (Acacia Senegal, Acacia greggii) and ginger (Zingiber officinale) each have cardioactive compounds and potentiate the effects of digoxin,[101] thereby increasing the possibility of adverse effects. Multiple herbal medicines have additive or synergistic effects when used in conjunction with commercial antibiotics.[102]

In contrast, Piper methysticum (kava kava) is antagonistic to levodopa function, significantly reducing its efficacy.[97] The affects of Ephedra (Ephedra sinica) on drug function are more complex. Ephedra has additive effects on several decongestants and stimulants, increasing stimulation, heart rate and the possibility of palpitations.[103] In contrast, Ephedra antagonises the effects of antihyopertensives and beta blockers, increasing the blood pressure.

Theoretical interactions

Studies into herb-drug interactions are still in their infancy. Therefore, many potential drug interactions are yet to be examined. However, several potential interactions are considered likely. For example, Neem (*Azadirachta indica*) has an antidiabetic effect by decreasing blood glucose levels.[104] Therefore, it may have an additive effect with other herbal drugs which have similar effects (eg. ginseng, garlic). If this is determined to be the case, concurrent treatment with 2 or more of these medicines could cause hypoglycaemia. However, at present this effect has not been investigated and is only theoretical.

PRECAUTIONS USING HERBAL MEDICATIONS IN SPECIAL CIRCUMSTANCES

Precautions also need to be taken in specialised circumstances and in patients with various medical conditions. Different individuals will metabolise drugs at different rates or metabolise the drugs to produce different products. This is dependent on a number of factors including genetic variations, environmental factors and the general health and well being of the patient. Patient

health in turn may be related to gender, age and different disease or physiological states. It is therefore important when using or prescribing herbal medicines to be aware of these factors and to take them into account when assessing the safety and suitability of herbal medicines.

Genetically Determined Drug Susceptibilities

A number of factors may affect an individual's vulnerability or resistance to herbal medications. Genetic variation between individuals may have a profound effect on an individual's responses to both herbal preparations and allopathic medicines. Inherited factors influence the effects of many common medications. Even 'recreational' drugs such as alcohol affect individuals to different extents, so that adverse effects may only be experienced by certain segments of a population. For example, some eastern Asian people have a genetic polymorphism that results in a lower activity of an enzyme that metabolises alcohol.[105] These individuals display symptoms including facial flushing, increased heart rate, muscular weakness and discomfort following alcohol consumption. Genetic factors may influence the rate at which a patient can metabolise a drug and therefore how effective that drug is. Approximately 10% of some racial groups lack the enzyme glucose-6-phosphate dehydrogenase, which is required for the metabolism of some herbal medicines (e.g. *Salix caprea*, which is commonly used in Ayuvedic medicine) as well as some allopathic medicines (e.g. the antimalarial drugs chloroquine and primaquine).[106] Individuals lacking glucose-6-phosphate dehydrogenase should not take these medicines as these drugs will persist in their bodies and may cause haemolysis, resulting in serious health problems.

The incidence of oral cancer in betel (*Piper betel*) chewers is also genetically influenced. Some individuals lack the ability to produce the enzyme CYP P450 2A6. This enzyme metabolises compounds in betel leaf to produce carcinogenic metabolites.[107] Therefore, individuals with low expression of this enzyme only produce low levels of carcinogens from the betel, whilst individuals with high expression levels of the enzyme produce high levels of carcinogens and therefore have a correspondingly higher risk of oral cancer.[107] Furthermore, some people have a genetic variation called CYP P450 1A1 exon 7 polymorphism. This variation results in the production of an enzyme that produces higher levels of carcinogen, thus a correspondingly higher incidence of oral cancer.[108]

Age Determined Drug Susceptibilities

The usage of medicines (both herbal and allopathic) is higher in certain age groupings. Older people (over 65 years of age) tend to use more pharmaceuticals and herbal medications than any other age group due to aging associated medical conditions and deteriorating health.[109] Often, elderly people are treating several disease states simultaneously and therefore regularly take multiple medications. As a result of their higher drug usage, older people also have a higher risk of cross-reactivities between medicines.

Furthermore, older people are often more sensitive to drugs than younger people due to the deterioration in the function of their vital organs. In individuals with decreased kidney function, drug excretion may be slower than in younger individuals. As a result, drugs may be excreted more slowly by elderly people and subsequently there is a risk of drug accumulation and the associated toxic effects. Similarly, when hepatic function is decreased, the metabolism of drugs may also be reduced with similar consequences. The blood vessels and cardiac tissue of the elderly have often deteriorated over time, resulting in the degeneration of cardiac cells and the loss of elasticity in blood vessels. Therefore, drugs that affect cardiac function and blood circulation have higher risks in elderly people and should be closely monitored. Drugs such as digoxin for example, which is used to control heart rate (particularly in irregular or rapid arterial fibrillation), may have a higher risk of adverse effects (e.g. dangerously low blood pressure and/or the alteration of heart rhythm) in elderly people.[109] Elderly patients are also often more sensitive to drugs that act on the nervous system (e.g. painkillers and sedatives) due to accumulated loss or damage to neurons throughout their lifetime. Similarly, elderly people may have developed defects in the production and/or effects of neurotransmitters (e.g. Parkinson's Disease) which may result in similar drug sensitivities, or conversely, drug tolerances.

It is important when prescribing medications for older people to adhere to several principles. Firstly, only medications with well documented mechanisms/ side effects should be prescribed. Furthermore, it is recommended that older people are initially prescribed a lower dosage than would be prescribed in younger individuals. The dosage may be increased at a later time if required, when the effects in the individual are known. The effects in the patient should also be carefully monitored until a safe but effective medication and dosage are determined. Patients who experience side effects including dizziness, loss of balance or blurred vision (falls may have serious consequences in older people), loss of mental acuity, changes in sleep patterns, mood changes, constipation, stomach complaints and diarrhoea, incontinence, rashes or other new symptoms, should consult a physician immediately.

Table 3: Age related susceptibilities and precautions using herbal drugs.

Medicine	Species or Active Agent	Medicinal Effect	Adverse Effect	Ref.
Asafoetida	*Ferula assafoetida*	antispasmodic, carminative, digestive, aid, expectorant, laxative, sedative, analgesic, antiseptic, aphrodisiac	causes methaemoglobinaemia	111
Bint al dhahab	contains lead oxide	treatment of stomach ailments	associated with encaphalitis and neurological deficits	29
Blue cohosh	*Caulophyllum thalictroides*	stimulant, tonic, antispasmodic, vermifuge, diuretic, treatment of rheumatism and inflammation	slows heart rate, decreases blood pressure, has oestrogen like hormonal activity, contains salicylates	111
Eucalyptus oil	Various species of Eucalyptus	antiseptic, astringent, antispasmodic, tonic, experctorant, stimulant, deodorant, febrifuge	may cause indigestion, muscular weakness, nausea, vomiting, diarrhoea, kidney damage. Should not be used internally or on broken skin	111, 140, 141
Germander	*Teucrium chamaedrys*	anti-inflammatory, diuretic, stomach disorders, appetite stimulant, tonic astringent, carminative, stimulant	may cause liver damage	111
herbs with alkaloids	various	various	toxic, may cause organ damage, particularly hepatic damage.	111
herb medicines containing metals	various	various	toxic, may cause organ damage, particularly brain, nerve and hepatic damage	111
Jin bu haun	Cordalis spp.	analgesic, sedative, used to treat heart and liver disease, useful in treating drug addiction	slows heart rate (bradycardia), causes respiratory and central nervous system depression, toxic	122
Groundsel	*Senecio vulgaris*	anthelmintic, epilepsy, treatment for kidney stones	toxic, causes liver disease, contain pyrrolizidine alkaloids	139
Comfrey	*Symphytum officinale*	brocchial problems, arthritis, ulcers, burns, acne and other skin disorders	contains alkaloids, may cause liver disease	52, 121
Thunder vine	*Tripterygium wilfordii*	treatment of autoimmune disorders including arthritis, systemis lupus, antitumour	powerful immunosuppressant effects	138
Neem	*Azadirachta indica*	antiseptic, anti-inflammatory, treatment of ulcers, stomach disorders, psoriasis, dandruff, jaundice, kills intestinal worms, malaria, viral diseases, sore throats, diabetes, anti-inescticidal	may cause toxic encephalopathy	111
St. John's wort	*Hypericum perforatum*	sedative, treatment of depression	multiple drug interactions, increases blood pressure, can cause confusion, agitation and drowsiness, may cause rejection of tissue transplants, may increase metabolism of other drugs	124

Herbal medicines (and allopathic drugs) should also be used cautiously in children. The rates of absorption, drug distribution and metabolism, as well as the excretion of drugs and their metabolites, are different in children than in adults. (Table 3) summarises some of the medications that should be used cautiously in children. Children have relatively large livers compared to adults, so may be more efficient in detoxifying and removing some toxic compounds from the body. Therefore, drugs that may be useful in adults may have limited beneficial effects in children due to their rapid clearance. An alternative may be to use lower doses more frequently in children than in adults. However, as with the usage of medications in older people, the effects of herbal medicines in children should be carefully monitored. The lower size and body mass of children generally means that they will not be

able to tolerate the same doses that would be prescribed to adults. Children also have developing immune systems and nervous systems which makes them more sensitive to the adverse effects of some medicines.

A further potential danger when using medications (both herbal and allopathic) in children is the inadequate testing of a medication in young individuals. Even with allopathic drugs which have a far better record of testing than herbal medicines, most testing occurs in adults. There are obvious ethical issues associated with testing medications in children. However, this often means that medicines that are widely used in children have not been adequately tested in children. Prescribed dosages in children are often based solely on their body mass compared to an adult, rather than on an understanding of absorption, distribution and clearance. This may impact dramatically on the effectiveness and safety of the medicine. Rigorous testing of herbal medicines for the use by children is even rarer. Therefore, caution should always be used when using herbal medicines in children.

Susceptibilities in Patients with Existing Health Complaints

Patients with existing medical conditions should consult a physician before beginning treatment with any medication as some medicines may have different effects in multiple organs. In the following sections, some of the factors patients with medical conditions and prescribers of herbal medicines should be aware of when beginning treatment are discussed. The effects of herbal treatments in patients with diabetes, heart disease and hepatic jaundice are examined to illustrate the susceptibilities of patients with existing illnesses to herbal drugs. This is by no means a complete listing of health complaints that may be affected by herbal medications but merely serves to highlight the need for greater understanding of the mechanisms of action of herbal medications.

Diabetes

More than 400 plants have been identified as being capable of lowering blood glucose levels. Indeed, prior to the development of insulin injections, diabetes was treated with a myriad of herbal medications including rehmannia (*Rehmannia glutinosa*)[110,111] and American ginseng (*Panax quinquefolius*).[111] Unripe bitter melon (*Momordica charantia*)[112] and *Gymnema sylvestre*[113] were used in traditional Asian medicinal systems as remedies for diabetes. Similarly, several Aloe species including *Aloe vera*[12,73] and fenugreek (*Trigonella foenum-graecum*)[111] were used in the Middle East as anti-diabetes drugs. In Latin American regions, the pads and fruit of prickly pears (Opuntia spp.) were used as traditional anti-diabetic treatments.[111] Scientific studies have demonstrated that prickly pear phytochemicals increase cellular sensitivity to insulin.[114] Native Americans used devils club (*Oplopanax horridus*),[115] barberry (Berberis spp.),[111] alum root (Heuchera spp.),[111] Joe Pye weed (Eutrochium spp.),[111] red trillium (*Trillium erectum*),[111] bugleweed (*Lycopus virginicus*)[111] and flowering spurge (*Euphorbia corollata*)[111] amongst other plants to treat diabetes. Noni (*Morinda citrifolia*) juice is a traditional Polynesian cure for diabetes.[116] Convervsely, elecampane (*Inula helenium*),[111] Indian pennywort (*Hydrocotyle asiatica*),[111] liquorice (*Glycyrrhiza glabra*)[111] and rosemary (*Rosmarinus officinalis*)[111] have been reported to increase blood glucose levels and should therefore be avoided by individuals suffering from diabetes. (Table 4) summarises some of the herbal medicines that may be used to treat diabetes as well as their side effects. The table also lists some herbal medicines which should be avoided by individuals with diabetes.

Arguably, the main concern with using herbal medications for the treatment of diabetes (apart from the lack of scientific evidence to support the efficacy of many such medications) is that many herbal medicines are adulterated with allopathic drugs. These adulterants may affect other medications that the patient is also taking for the treatment of their diabetes. Therefore, it is possible that any traditional medicine may have profound effects on the control of blood glucose levels. It is important that any diabetic patient using allopathic medicine should inform their physician of any herbal medications they are also taking (including those taken for reasons other than their diabetes) so the possibility of contraindication or cross-reactivity can be assessed.

Heart Disease

Many herbal preparations have cardio-pulminary effects which may be dangerous to persons with heart disease (Table 5). Some medications directly increase the heart rate. Belladonna (*Atropa belladonna*),[111] a plant used in traditional medicine systems to treat headaches, menstral pains, peptic ulcers, inflammation and motion sickness, contains tropane alkaloids which increase the heart rate. Ginger (*Zingiber officinale*)[111] and ginseng (Panax spp.)[111] are known to increase blood pressure. Yohimbe (*Pausinystalia yohimbe*) contains an alkaloid called yohimbine which stimulates the sympathetic nervous system, resulting in elevated blood pressure.[117] Yohimbe also induces increased levels of adrenaline and noradrenaline, which may result in arrhythmias in some individuals. Ephedra (*Ephedra sinica*), a constituent of many herbal medicines, has a similar effect on the sympathetic nervous system.[111] It has been reported to cause arrhythmia and even myocardial

Table 4: Adverse reactions to herbal drugs and drugs which should be avoided or closely monitored in people with diabetes mellitus.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Aloe	various Aloe species including *Aloe ferox Aloe barbadensis,*	antiseptic, immune stimulator, anti-inflammatory, treatment of diabetes purgative, tonic	May be effective in the treatment of diabetes but caution should be used as it is a strong purgative and may causevomiting	12, 73, 111
Alum root	Heuchera spp.	Styptic, astringent, used to treat dysenrty, diarrhoea, sore throat, wounds and abrasions, stomach ailments, eye wash	May be effective in the treatment of diabetes but caution should be used as it can also cause gastric problems as well as kidney and liver failure.	111
American ginseng	*Panax quinquefolius*	stress reduction, improves vitality may be useful in the treatment of diabetes	May be effective in the treatment of diabetes but caution should be used as it may result in increased blood pressure and headaches, fever, should also be avoided both those suffering from inflammatory conditions or obesity	111
Barberry	Berberis spp.	tonic, purgative, antiseptic, anthelmintic,	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111
Bitter melon	*Momordica charantia*	antihelmintic, antimalarial, antiviral, cardioprotective, possible anticancer properties, used to treat diabetes, colic dysentry	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	112
Bugleweed	*Lycopus virginicus*	sedative, astringent, narcotic, tonic	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111
Devils club	*Oplopanax horridus*	treatment of diabetes and tumours,	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111
Elecampane	*Inula helenium*	anthelmintic, antispasmodic, analgesic, diuretic, expectorant, stimulant, tonic, carminative, antiseptic, laxative	increases blood glucose levels, should be avoided by patients with diabetes	111
Fenugreek	*Trigonella foenum-graecum*	arthritis, induces lactation, treatment of diabetes	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111, 121
Flowering spurge	*Euphorbia corollata*	purgative, laxative, emetic, used to treat rheumatism, diabetes, snakebite, warts	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic may even cause blistering of the skin on contact. Should ony be used with medical supervision	111
Indian pennywort	*Hydrocotyle asiatica*	antipyretic, febrifuge, antispasmodic, sedative, tonic, central nerve system stimulant, used to treat rheumatism, neuralgia, blood disorders, heart disorders, sore throat, coughs, colds, allergies, hepatitis, venereal diseases, epilepsy, insomnia, leprosy, psoriasis	increases blood glucose levels, should be avoided by patients with diabetes	111
Joe Pye weed	Eutrochium spp.	diuretic, stimulant, tonic, astringent, kidney disorders, neuralgia, rheumatism, impotence, diabetes, headache, colds	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111
Liquorice	*Glycyrrhiza glabra*	cough, peptic ulcer, treatment of arthritis and other auto-immune disorders	increases blood glucose levels, should be avoided by patients with diabetes	111

Noni	*Morinda citrifolia*	possible anticancer properties, antiinflammatory	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	116
Prickly pear	Opuntia spp.	treatment of diabetes, hangover	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	114
Red trillium	*Trillium erectum*	antiseptic, astringent, expectorant, tonic, used to treat coughs and bronchial problems, asthma, difficult breathing, diarrhoea, dysentry, skin conditions	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	111
Rehmannia	*Rehmannia glutinosa*	tonic, rheumatism, gout, antiinflammatory properties, impotence, hair loss, hypertension, menopause, diabetes	May be effective in the treatment of diabetes but caution should be used as it contains compounds which may be toxic	110, 111
Gudmar	*Gymnema sylvestre*	treatment of diabetes, obesity, anemia, high cholesterol, digestive disorders, liver disease	appears to stimulate insulin production as well as blocking hepatic glucose production, however only useful in type 2 diabetes. However caution should be used as it contains alkaloids and saponins which may be toxic.	113
Rosemary	*Rosmarinus officinalis*	stimulant, carminative, antispasmodic, reduces blood pressure, used to treat nerve disorders, digestive disorders, palsy, dizziness, migraine, headache, colic, menstrual pains, eczema	increases blood glucose levels, should be avoided by patients with diabetes	111

infarction (heart attack). Liquorice (*Glycyrrhiza glabra*)[111] treatment may induce the production of mineralocorticoids resulting in the retention of sodium and water. This may result in increased blood pressure, hypertension and pulmonary edema (which results in difficulty in breathing). Many other plants should also be avoided as they may disturb the heart rhythm and cause arrhythmias. These include foxglove (*Digitalis purpurea*), dogbane (*Apocynum cannabinum*), wolfsbane (*Aconitum lycotonum*), monkshood (*Aconitum napellus*), lilly of the valley (*Convallaria majalis*), wallflower (*Cheiranthus cheiri*),[111] oleander (*Nerium oleander*)[111,118] and red squill (*Urginea maritime*).[119]

Hepatic Jaundice

Hepatic jaundice can result from acute hepatitis, hepatotoxicity and various other liver diseases (including alcoholic cirrhosis). Patients with hepatic jaundice have a reduced ability to metabolise and excrete bilirubin, resulting in increased serum bilirubin levels. Because bilirubin has low solubility in aqueous solutions (such as the blood stream), it is transported throughout the body bound to albumin. Herbal medications which act to displace bilirubin from serum albumin should be avoided (Table 6). Indeed, studies have shown that *Artemisia scoparia*, which is highly effective at displacing biliribin, may have serious negative medical implications in individuals with hepatic jaundice.[120] This study also linked displaced bilirubin to brain damage in jaundiced infants. Of concern, *Artemisia scoparia* is regularly prescribed in TCM to treat the symptoms of hepatic jaundice. Thus, treating the condition with this herb may be causing far greater damage than not treating the condition. Similarly, Chinese goldthread (*Coptis chinensis*), a TCM used to treat inflammation, is also a potent bilirubin displacer.[111] Studies have linked *Coptis chinensis* with kernicterus (bilirubin associated brain damage).

Individuals with hepatic jaundice should also avoid herbal medications containing hepatotoxins (Table 6). Comfrey (Symphytum officinale) contains alkaloid components which cause occlusion of the small veins in the liver, resulting in cirrhosis and eventually liver failure.[52,121] Its usage should be avoided by patients suffering from hepatic jaundice. Non-infectious hepatitis has also been linked to various medicinal plants including chaparral (Larrea tridentate),[111]

Table 5: Adverse reactions to herbal drugs and drugs which should be avoided or closely monitored in people with cardiac conditions.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Belladonna	*Atropa belladonna*	antispasmodic, diuretic, narcotic, sedative, possible anticancer activity	contains tropane alkaloids which increase heart rate	111
Dogbane	*Apocynum cannabinum*	cathartic, emetic, expectorant, tonic, laxative, used in the treatment of fever, dyspepsia, gall stones, liver disorders,	affects the heart rhythm and may cause arrhythmias	111
Ephedra	*Ephedra sinica*	stimulant, weight loss, treatment of asthma, allergies, cold	increases blood pressure, may cause arrhythmias	111
Foxglove	*Digitalis purpurea*	used to regularise and slow heartbeat and to increase blood pressure, also powerful diuretic, treats headaches and inflammation	affects the heart rhythm and may cause arrhythmias	111
Ginger	*Zingiber officinale*	nausea, arthritis	increases blood pressure	111
Ginseng	Panax spp.	stress reduction, improves vitality	increases blood pressure	111
Lilly of the valley	*Convallaria majalis*	antispasmodic, diuretic, emetic, laxative, tonic, cardiac disorders, treatment following strokes, reduces blood pressure, treatment for epilepsy, palsy, headache, gout, heart disorders	affects the heart rhythm and may cause arrhythmias	111
Liquorice	*Glycyrrhiza glabra*	cough, peptic ulcer, treatment of arthritis and other auto-immune disorders	induces water retention which may result in increased blood pressure, hypertension and pulmonary oedema	111
Monkshood	*Aconitum napellus*	analgesic, cardiotonic, febrifuge, stimulant, used to treat neuralgia, sciatica, gout, rheumatism, fever and skin conditions	affects the heart rhythm and may cause arrhythmias	111
Oleander	*Nerium oleander*	dermatitis, eczema, psoriasis, skin sores, warts, ringworm, asthma, epilepsy, malaria, antitumour, gingivitis, cardiac failure (in some doses), diabetes, immunostimulant	affects the heart rhythm and may cause arrhythmias	111, 118
Red squill	*Urginea maritime*	cardiac stimulant (at low doses), diuretic, emetic, due to its toxicity it is also useful as a rodenticide and an insecticide	affects the heart rhythm and may cause arrhythmias	119
Wallflower	*Cheiranthus cheiri*	cathartic, emetic, expectorant, tonic, laxative, used in the treatment of fever, dyspepsia, gall stones, liver disorders,	affects the heart rhythm and may cause arrhythmias	111
Wolfsbane	*Aconitum lycotonum*	analgesic, cardiotonic, febrifuge, stimulant, used to treat neuralgia, sciatica, gout, rheumatism, fever and skin conditions	affects the heart rhythm and may cause arrhythmias	111
Yohimbe	*Pausinystalia yohimbe*	treatment of erectile dysfunction and obesity	contains an alkaloid which increases blood pressure, causes arrhythmias	117

germander (Teucrium chamaedrys),111 jin bu huan (Lycopodium serratum),[122] lobelia (Lobelia inflata), mistletoe (Phoradendron flavescens)[111] and penny royal (Mentha pulegium).[52,111,121]

HERBAL MEDICINES TO AVOID PRIOR TO SURGERY

Individuals scheduled to undergo a surgical procedure would be advised to seek advice from their physician regarding whether a particular medicine should be discontinued prior to surgery. Advice should be sought as soon as the patient becomes aware of the pending surgery as some compounds may take considerable time to clear from the body and stopping their usage a week or more before surgery may be necessary. At the very least, the patient should notify the surgeon of any medications (including herbal medicines) that they are taking, to avoid cross-reactivity with the drugs and anaesthetics

administered during the surgery, and to lessen the chances of toxicity. Some medications should not be discontinued abruptly, but instead reduced gradually prior to surgery to lessen the impact. For example, guarana (Paullinia cupana) (which contains caffeine) is regularly consumed in many parts of South America. It is also becoming increasingly available in Western countries through its inclusion in 'energy drinks'. Sudden withdrawl of guarana in chronic users may result in symptoms including anxiety, headache and irritability.[123] Similarly, abruptly ceasing feverfew treatment (Tanacetum parthenium syn. Chrysanthemum parthenium), a herb traditionally used for reducing fevers as well as treating headaches, arthritis and digestive problems, often results in severe recurrent headaches.[124,125] Such medications should instead be decreased over a period of time prior to the surgery.

Herbal medicines may have adverse effects during and after surgery in multiple ways (Table 7). Danshen (Salvia miltiorrhiza), dang gui (Angelica sinensis) as well as herbal preparations containing chamomile (Matricaria recutita) are known to increase bleeding during and after surgery.[111,124,125] Other herbal medicines including alfalfa (Medicago sativa), ginkgo biloba, ginseng, garlic (Allium sativum) and liquorice (Glycyrrhiza glabra) interfere with coagulation, also increasing blood loss.[124,125] Some of these herbal medicines may also delay the wound healing process. Other herbal medications may interfere with anaesthesia, either lessening (e.g. ephedra (Ephedra sinica))[124] or potentiating its effect (e.g. feverfew),[124,125] thereby delaying recovery. Other herbal medications (e.g. black cohosh, ephedra, ginseng, liquorice, St John's wort) may induce dangerous changes to the pulse rate, blood pressure and heart rhythm thereby potentiating the toxicity of some anaesthetics.[124] Some other medications may alter the immune response. Echinacea is known to stimulate the immune system and could therefore potentially promote organ rejection following transplant surgery.[126,127] Alternatively, medications decreasing the immune response would be expected to increase the likelihood of post-operative infections. Herbal medicines may also effect the function of surgical and post-operative drugs by altering their metabolism. For example, St John's wort may induce changes in CYP P450 enzymes, resulting in unpredictable changes in the levels and activity of surgical and post-operative drugs.[124] Taking many other herbal medications with surgical drugs can cause post-operative discomfort (e.g. ginseng, garlic).[124,125]

Herbal Medicines to Avoid During Pregnancy

In an effort to avoid drugs, pregnant women often use herbal medicines in the belief that they are harmless. Many herbal agents are considered as dietary supplements and are often openly sold through health food stores. Whilst for herbal medicine users this may reinforce the idea that these herbal preparations are harmless, it also often makes them exempt from premarketing drug safety and efficacy standards that are required of allopathic medications. As a result, the purity and dosage of the active compounds as well as their efficacy, side effects and cross-reactivities are often not known for herbal medicines. Furthermore, relatively little scientific information is available on the effects of herbal medicines during pregnancy. Whilst many herbal medicines have been used during pregnancy for hundreds (or even thousands of years), little effort has been made to scientifically monitor the safety of these preparations over this time. Indeed, the lack of reported adverse effects for some medicines over such long periods is often touted by some herbal medicine adherents as proof of their safety. However, lack of reported negative accounts does not necessarily ensure that a medication is safe. Difficulties exist in scientifically evaluating a drug during preganacy. For obvious reasons, it is impossible for manufacturers to undertake pre-market trials of medications in pregnant women. Often, the only information available on the effects of herbal medicines comes from studies in animals. Pregnant female animals are often given doses high enough to cause adverse effects in an adult. It is impossible to interpret the potential risk to a fetus from such studies. Furthermore, these animal studies may not adequately determine a risk to humans.

Another major concern is that herbal medications are often used without the physicians knowledge by women who do not realise their potential harm. Furthermore, some patients may misinterpret dosage instructions (if such instructions come with the medication) and therefore take higher or more frequent doses than required, resulting in excessive exposure to both the mother and the fetus. A medication which is otherwise considered safe, may have harmful effects in such situations. Herbal (as well as allopathic) medications to be avoided during pregnancy are those that promote menstruation (and thus abortions), those that promote smooth muscle contractions (e.g. laxatives, essential oils) which may adversely affect the developing fetus, as well as those that have direct or indirect effects on the fetus itself. This last group may include drugs which are toxic to the fetus, those that cause fetal malformations (mutagens and teratogens) and those that induce hormonal effects that may negatively impact on the fetus (e.g. hormones that feminise male foetuses or conversely, those that masculinise female foetuses). (Table 8) summarises some of the herbal medications which should be avoided by pregnant women.

Table 6: Adverse reactions to herbal drugs and drugs which should be avoided or closely monitored in people with hepatic jaundice.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Redstem wormwood	*Artemisia scoparia*	antiseptic, antithelminic, antispasmodic, carminative, febrifuge, narcotic, tonic, stimulant	displaces serum bilirubin from serum ablumin, may result in brain damage further hepatic dysfunction	111, 121
Chaparral	*Larrea tridentate*	laxative, antitumour, antioxidant, skin disorders, diarrhoea, warts, mouthwash	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	111
Chinese goldthread	*Coptis chinensis*	general tonic, sedative	displaces serum bilirubin from serum ablumin, may result in brain damage further hepatic dysfunction	111
Comfrey	*Symphytum officinale*	brocchial problems, arthritis, ulcers, burns, acne and other skin disorders	contains alkaloids, may cause liver damage	52, 121
Germander	*Teucrium chamaedrys*	anti-inflammatory, diuretic, stomach disorders, appetite stimulant, tonic astringent, carminative, stimulant	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	111
Jin bu huan	*Lycopodium serratum*	analgesic, sedative, used to treat heart and liver disease, useful in treating drug addiction	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	122
Lobelia	*Lobelia inflata*	antispasmodic, diuretic, emetic, sedative, expectorant, stimulant, treatment of asthma, whooping cough, ringworm, sore throats, bronchitis, pneumonia, vomiting, skin irritations, epilepsy	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	111
Mistletoe	*Phoradendron flavescens*	emetic, diuretic, stimulant, vasodilator, cardiac disorders, narcotic, antispasmodic	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	111
Penny royal	*Mentha pulegium*	carminative, antispasmodic, sedative, stimulant, rubrifacent	contains compounds which may cause liver damage and should not be used by individuals with liver maladies	52, 111, 121

Table 7: Herbal drugs which should be avoided prior to surgery.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Alfalfa	*Medicago sativa*	treatment of digestive and kidney disorders, arthritis and inflammation	prolongs coagulation time	124, 125
Black cohosh	*Actaea racemosa*	menopause, cardiovascular disease	slows heart rate, decreases blood pressure, has oestrogen like hormonal activity, contains salicylates	124
Chamomile	*Matricaria recutita*	treatment of anxiety, stomach ailments, colds, muscular aches, insomnia	increases bleeding inhibits the effects of benzodiazapines	111, 124
Dang gui	*Angelica sinensis*	treatment of gynecological disorders, fatigue, high blood pressure. Has analgesic, antispasmodic, antiinflammatory and sedative effects	increases bleeding	111, 124
Danshen	*Salvia miltiorrhiza*	treatment of cardiovascular and cerebrovascular diseases, renal failure, diabetes	increases bleeding	79

Echinacea	*Echinacea purpurea*	stimulates immune system, colds, infections, laxative	stimulates immune systems so could interfer with immunosuppresive therapy, may result in transplant rejection	126, 127
Ephedra	*Ephedra sinica*	stimulant, weight loss, treatment of asthma, allergies, cold	increases heart rate and blood pressure, causes arrhythmias, may block cardiac blood supply, may interfer with anaesthesia	124
Evening primrose	*Oenothera biennis*	treatment of bruises, speeds wound healing	reduces platelet aggregation and blood clotting	125
Feverfew	*Tanacetum parthenium*	migraine, arthritis, fever, digestive problems	increases bleeding, anxiety, insomnia, reduces platelet aggregation and blood clotting	124, 125
Garlic	*Allium sativum*	arteriosclerosis, hypertension, fever, hypercholesterolemia, infection	reduces blood clotting, may increase post-operative bleeding	124, 125
Ginger	*Zingiber officinale*	nausea, arthritis	heartburn and discomfort, may affect anaethesia	124
Ginko	*Ginko biloba*	cardiovascilar disease, improves memory	reduces platelet aggregation and blood clotting, additive anticoagulant effect with aspirin, increases bleeding	124
Ginseng	several species of the genus Araliaceae	stress reduction, improves vitality	increases bleeding, increases arrhythmias, increases blood pressure increases heart rate, induces hypoglycaemia	124
Goldenseal	*Hydrastis canadensis*	treatment of gastritis, infection, dysmenorhea	increases blood pressure	124
Kava kava	*Piper methysticum*	treatment ofanxiety, stress, muscular pain, insomnia	inhibits blood coagulation, interacts with multiple drugs, increases the effect of anaesthetics	124
Kudzu	*Pueraria lobata*	control of postmenopausal symptoms, treatment of tinnitus and vertigo, liver detoxification, heart disease and circulatory disorders	increases post-operative bleeding	125, 142
Liquorice	*Glycyrrhiza glabra*	cough, peptic ulcer, treatment of arthritis and other auto-immune disorders	prolongs coagulation time, increases blood pressure, causes electrolyte imbalance, induces arrhythmias	124
St John's wort	*Hypericum perforatum*	sedative, treatment of depression	multiple drug interactions, increases blood pressure, can cause confusion, agitation and drowsiness, may cause rejection of tissue transplants, may increase metabolism of other drugs	124
Valerian	*Valeriana officinalis*	insomnia, anxiety, migraine, pain relief	may increase the effects of other drugs,	111, 124

Herbal medications that promote menstruation (emmenagogues) and those that promote smooth muscle contractions should be avoided throughout all stages of pregnancy as contractions of the uterus may cause miscarriages. Many herbal medicines, including vervain,[111] yarrow,[111,121] turmeric,[111] mandrake,[128] catnip,[111,121] guggul,[129] mayapple[130] and senega[111] may promote menstruation and should be avoided by pregnant women. Laxatives induce increased uterine activity which may be harmful to the fetus. Anthraquinone containing medications (e.g. rhubarb, Aloe vera),[12,73,111] are laxatives and uterus stimulants which may induce miscarriage in pregnant women. Other herbs with well documented stimulant effects on uterine muscles include blue cohosh,[111] betony,[111] capsicum and cayenne,[111,121] devil's claw,[111] fenugreek,[111,121] golden seal,[111] liquorice,[124] nettle[111] and wormwood.[111,121]

Table 8: Herbal drugs which should be avoided during pregnancy.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Alfalfa	*Medicago sativa*	treatment of digestive and kidney disorders, arthritis and inflammation	estrogenic effects	124
Aloe	various Aloe species including *Aloe ferox Aloe barbadensis,*	antiseptic, immune stimulator, anti-inflammatory, treatment of diabetes	laxative	12, 73, 111, 143, 144
American mandrake	*Podophyllum peltatum*	relieves skin irritations, treatment of intestinal worms, increases perspiration treatment of warts	uterine stimulant, emmenagogue	128
Anise	*Pimpinella anisum*	Carmative, insecticide	estrogenic effects	131, 132
Arnica	*Arnica montana*	antiseptic, anti-inflammatory, stimulates wound healing, decongestant	Estrogenic effects in the fetus irritant	111
Beth root	Trillium spp.	treatment of coughs, bronchial disorders, asthma, difficulty breathing, diarrhoea, dysentry, insect bites and stings, ulcers, inflamation, menopause, aphrodisiac	uterine stimulant	111
Betony	*Stachys officinalis*	asthma, bronchitis, heartburn, kidney and bladder problems, excessive sweating, varicose veins	uterine stimulant	111
Black cohosh	*Actaea racemosa*	menopause, cardiovascular disease	uterine stimulant, estrogenic effects	136
Blood root	*Sanguinaria canadensis*	expectorant, stimulant, diuretic, febrifuge, sedative, antiseptic	uterine stimulant	111
Blue cohosh	*Caulophyllum thalictroides*	stimulant, tonic, antispasmodic, vermifuge, diuretic, treatment of rheumatism and inflammation	uterine stimulant	111
Borage	*Borago officinalis*	metabolic and hormonal regulation, gynecological disorders, menopause symptoms	may cause liver toxicity in infants	121
Broom	*Cytisus scoparius*	cathartic, diuretic	abortifacient	111
Buckthorn	*Rhamnus catharticus*	purgative	laxative	111
Butterbur	*Petasites officinales*	treatment of fever, headaches, allergies, stomachaches, stress and anxiety	hepatotoxic	111
Calamus	Acorus calamus	antispasmodic, carminative, emetic, decongestant,, expectorant, febrifuge, sedative, stimulant, tonic	uterine stimulant	111
Capsicum	Capsicum spp.	antiseptic, febrifuge, antiseptic, carminative, nerve tonic, stimulant, tonic, rubefacient, stimulates saliva secretion	uterine stimulant	111, 121
Carline thistle	*Carlina acaulis*	carminative, diuretic, febrifuge, aids digestion	uterine stimulant	111
Cascara sagrada	*Rhamus purshiana*	bitter tonic, purgative, emetic	laxative, emmenagogue	111
Catnip	*Nepeta cataria*	antispasmodic, carminative, nerve tonic, sedative, stimulant, general tonic	emmenagogue	111, 121
Cayenne	*Capsicum frutescens*	antiseptic, febrifuge, antiseptic, carminative, nerve tonic, stimulant, tonic, rubefacient, stimulates saliva secretion	uterine stimulant	111, 121
Celandine	*Chelidonium majus*	treatment of hepatic and renal disease, detoxification, treatment of skin conditions (including wounds, warts, psoriasis)	embryo toxin	111
Chamomile	*Matricaria recutita*	treatment of anxiety, stomach ailments, colds, muscular aches, insomnia	abortifacient, possible tetratigen	111
Chasteberry	*Vitex agnus-castus*	tonic, reproductive disorders, anti-aphrodisiac effects	uterine stimulant, antiandrogenic hormonal effects	145
Colt's foot	*Tussilago officinale*	astringent, emollient, tonic, expectorant, anti-inflammatory	carcinogenic, abortifacient	111
Cotton root bark	*Gossypium herbaceum*	aphrodisiac, parturient	emmenagogue, abortifacient	111

Cumin	*Cuminum cyminum*	antispasmodic, carminative, stimulant	abortifacient	111, 121
Devil's claw	*Acacia senegal, Acacia greggii*	demulcent, mucilaginous	uterine stimulant	111
Dock/Sorrel	*Rumex acetosa*	treatment of fever, diarrhoea, antiseptic, skin rashes	laxative	146
Ephedra	*Ephedra sinica*	stimulant, weight loss, treatment of asthma, allergies, cold	may cause fetal neuronal damage	111
Fennel	*Foeniculum vulgare*	carminative, decongestant, diuretic, antispasmodic, expectorant, stimulant, anti-inflammatory, relieves coughs	uterine stimulant	111, 121
Fenugreek	*Trigonella foenum-graecum*	expectorant, emollient, febrifuge, tonic, carminative, anti-inflammatory, stimulant, diuretic	causes uterine contractions	111, 121
Feverfew	*Tanacetum parthenium*	migraine, arthritis, fever, digestive problems	uterine stimulant	111
Flax seed	*Linum usitatissimum*	antiseptic, anti-inflammatory, emollient, laxative, purgative, tonic	uterine stimulant	111
Fucus (kelp)	Fucus spp.	aphrodisiac, treatment for hair loss, hyperthiroidism, obesity	abortifacient, hormonal effects	133
Garlic	*Allium sativum*	arteriosclerosis, hypertension, fever, hypercholesterolemia, infection	causes uterine contractions	111
Ginseng	several species of the genus Araliaceae	stress reduction, improves vitality	toxic to fetus	111, 121
Goldenrod	*Salidago odora*	astringent, carminative, diuretic, stimulant	abortifacient	111
Goldenseal	*Hydrastis canadensis*	treatment of gastritis, infection, dysmenorhea	uterine stimulant	111
Guggul	*Commiphora wightii*	decreases cholesterol synthesis	emmenagogue	129
herbs with alkaloids	various	various	embryotoxic/fetotoxic	111
Hops	*Humulus lupulus*	analgesic, antithelminic, diuretic, tonic, febrifuge, hypnotic, sedative, soporific, digestive disorders	hormonal effects (estrogenic)	111
Horehound white	*Marrubium vulgare*	antispasmodic, diuretic, expectorant, laxative, stimulant, tonic, stomach ache	laxative, abortifacient	111, 121
Horehound, black	*Ballota nigra*	relief of morning sickness	laxative, emmenagogue	111, 121
Horseradish	*Armoracia rusticana*	bronchitis, sinusitis, rheumatism, flu	hormonal effects	111, 121
Lady's mantle	*Alcemilla vulgaris*	treatment of hormonal disturbances, menstral disorders, headaches, dizziness, stomache ache, nausea, obesity	uterine stimulant, ellenagogue	111
Liquorice	*Glycyrrhiza glabra*	cough, peptic ulcer, treatment of arthritis and other auto-immune disorders	uterine stimulant, estrogenic effects	124
Madder	*Rubia tinctorum*	astringent, diuretic	possible mutagen	111
Magnolia flower	*Magmolia glauca*	astringent, febrifuge, stimulant, tonic antiperiodic	uterine stimulant	111
Malefern	*Dryopteris filix-mas*	antithelmintic, vermifuge, astringent	uterine stimulant	111
Mayapple	Lycopus spp.	astringent, sedative, treatment of anxiety and palpitations	emmenagogue	130
Meadow saffron	*Colchicum autumnale*	treatment of gout, arthritis, rheumatism	laxative, toxic	111
Mistletoe	*Phoradendron serotinum*	emetic, diuretic, stimulant, vasodilator, cardiac disorders, narcotic, antispasmodic	emmenagogue, uterine stimulant	111
Motherwort	*Leonurus cardiaca*	various cardiac and circulatory disorders, anxiety, carminative, muscle cramps, menstral problems, difficult breating, menopause, kidney disorders, rheumatism, sedative, hypotensive, sciatica, insomnia, colds, fevers, aids in childbirth	uterine stimulant, hormonal effects	111

Mugwort	*Artemisia vulgaris*	antispasmodic, kills intestinal worms, antiseptic, purgative, hemostatic	abortifacient	111
Nettle	*Urtica dioica*	rheumatism, anti-inflammatory, mild laxative, treatment of hepatic disease and obesity	uterine stimulant, diuretic	111
Oregon grape	Berberis spp.	diuretic, laxative, tonic	uterine stimulant	111
Parsley	*Petroselinum crispum*	good source of vitamin c, treatment of asthma, anemia, obesity, rheumatism tooth ache, indigestion, intestinal parasites	uterine stimulant	111, 124
Passion flower	*Passiflora incarnata*	antispasmodic, hypnotic, sedative, nerve tonic	uterine stimulant, emmenagogue	111
Pennyroyal	*Mentha pulegium*	carminative, antispasmodic, sedative, stimulant, rubrifacent	uterine stimulant, emmenagogue hepatotoxic	52, 111, 121
Periwinkle	*Vinca major, Vinca minor*	astringent, sedative, nerve tonic, antitumour properties	uterine stimulant, emmenagogue	111
Pokeroot	*Phytolacca americana*	anti-inflammatory, anti-syphilitic, emetic, cathartic	uterine stimulant, emmenagogue	111
Red clover	*Trifolium pratense*	diuretic, expectorant, antispasmodic, anti-tumour, stimulant	estrogenic effects	111
Rhubarb	*Rheum officinale*	laxative, purgative, astringent, tonic, antipyretic, hemostatic	uterine stimulant, emmenagogue	111
Rue	*Ruta graveolens*	carminative, stimulant, antithelminic, tonic, stomach disorders, antispasmodic	emmenagogue	111
Sage	*Salvia officinalis*	carminative, stimulant, diuretic, antispasmodic, expectorant, tonic, antiseptic, treatment of diarrhoea	uterine stimulant	111, 121
Sassafras	*Sassafras officinale*	stimulant, diuretic, antiseptic arthritis, gout, general tonic, skin disorders	possible carcinogen	111
Saw palmetto	*Serenoa serrulata*	antiseptic, cardiac disorders, diuretic, expectorant, tonic	estrogenic effects	111
Senega	*Polygala senega*	antispasmodic, cathartic, emetic, expectorant, stimulant	emmenagogue	111
Senna	Senna spp.	constipation	laxative, uterine stimulant, emmenagogue	52
Shepherd's purse	*Capsella bursa-pastoris*	treatment of muscle afflictions and circulatory disorders	emmenagogue	111
Slippery elm bark	*Ulmus rubra, Ulmus fulva*	astringent, diuretic, emollient, tonic, expectorant	abortifacient	111
Japanese pagoda tree (seed pods)	*Sophora japonica*	antiseptic, anti-inflammatory, diuretic, antispasmodic, emetic, emollient, febrifube, hypotensive, purgative, tonic	abortifacient	147
Squaw vine	*Mitchella repens*	astringent, diuretic, tonic	emmenagogue	111
Squill	Scilla spp.	expectorant, treatment of coughs	cardiac toxin	148
Tansy	*Crysanthemum balsamita*	cuts and wounds, swelling, used to treat liver disorders, headache, antiseptic	uterine stimulant, emmenagogue	111
Thuja	Thuja spp.	treatment of ringworm, warts, thrush	uterine stimulant, emmenagogue	149
Thyme	*tymus vulgaris*	toothache and stomach ache, antiseptic, expectorant, diarrhoea, parasitic worms asthma	uterine stimulant, emmenagogue	111, 121
Turmeric	*Hydrastis canadensis*	laxative, tonic,antiseptic, treatment of eye disorders, malaria, diuretic	emmenagogue	111
Vervain	*Verbena hastata*	emetic, expectorant, tonic, vermifuge, nerve tonic	emmenagogue, hormonal effects	111
Wild cherry	*Prunus serotina*	astringent, sedative, digestive aid, expectorant, diuretic, antispasmodic, carminative	uterine stimulant	111
Wormwood	*Artemisia absinthium*	antiseptic, antithelminic, antispasmodic, carminative, febrifuge, narcotic, tonic, stimulant	uterine stimulant	111, 121
Yarrow	*Achillea millefolium*	astringent, antispasmodic, tonic, promotes sweating, hemostatic, diuretic, carminative, treatment of stomache disorders	emmenagogue	111, 121

Several herbal medicines have hormonal effects. Plants may contain phytoestrogens similar in structure and/or function to the female hormone estrogen. Herbal medicines containing these compounds may induce a male fetus to develop female characteristics and features. Such plants include alfalfa (Medicago sativa),[124] aniseed (Pimpinella anisum),[131,132] black cohosh (Actaea racemosa), red clover (Trifolium pratense) and saw palmetto (Serenoa serrulata).[111] Conversely, herbal medications containing androgens have been shown to be capable of masculinising female fish[111] and could potentially have similar effects in human female foetuses. Other herbal medicines may contain compounds that inhibit or stimulate other hormone activities. Vervain (Verbena hastata) for example inhibits several hormones. Fucus spp.[133] and horseradish (Armoracia rusticana)[111,121] stimulate thyroid hormone activity whilst vervain is associated with the inhibition of sperm and ova production.[111]

Herbal Medicines to Avoid During Lactation/ Breastfeeding

Many of the same herbal medications that should be avoided during pregnancy should also be avoided during breast feeding (Table 9). Toxic compounds in medicines may be accumulated in the milk during lactation and these compounds are delivered directly to the infant when it feeds. In general, breastfeeding mothers would be advised to avoid any herbal medicines that contain pharmacologically active compounds. Medications which affect the nervous system in particular should be avoided. For example kava kava contains compounds which have a profound sedative effect.[124] It is thought that these same compounds may also cause damage to infant livers. Other medications that affect the nervous system may also cause damage to infant's nervous systems (e.g. dang gui (Angelica sinensis), Evodia danielli and ephedra).[111,124,134] Similarly, coltsfoot (Tussilago farfara)[135] and comfrey (Symphytum afficinale)[52,121] contain alkaloids which may accumulate in the liver resulting in liver damage. Other medications contain phytochemicals which may not cause tissue damage in infants, yet still make them ill. Aloe vera for example contains anthraquinones which may induce colic and diarrhoea in infants.[12,111,143,144] Black snakeroot (Fucus vesiculosus),[136] male fern (Dryopteris filix-mas,[111] elecampane (Inula helenium),[111,137] rhubarb (Rheum officinale)[111] and senna (Senna alexandrina)[52] should all be avoided by breastfeeding women for similar reasons. Medications with immunosuppressive effects (e.g. Tripterygium wilfordii) should also be avoided so as not to compromise the infants immune system.[138] Other herbs (e.g. anise (Pimpinella anisum)) may produce hormonal effects in infants, thereby affecting their development.[131,132]

Some herbal medications may also affect the milk supply in lactating women. Indeed, many women use herbal medications during breast feeding for the purpose of increasing their milk production. Fenugreek (Trigonella foenum-graecum) has been reported to have such an effect although scientific studies have shown that increased milk production only occurs if the mother takes high doses of the herb for prolonged periods.[121] This may also result in hypoglycaemia in the nursing mother. Furthermore, high maternal fenugreek ingestion (which contains coumarins and nicotinic acid) may result in an increase in the maternal heart rate and blood pressure. The effects of such high doses in infants is not as well known although fenugreek (which is related to peanuts) is likely to cause allergic reactions in breastfeeding babies. Fennel (Foeniculum vulgare) is another herb used to increase milk production.[111,121,131] However, fennel oil is extremely toxic and can cause convulsions and respiratory distress in infants, even in very low doses. The oil is also suspected of inducing hormonal effects in infants and may therefore affect development. Fennel should be completely avoided by nursing mothers. In contrast, some herbal medications used by nursing mothers for a variety of reasons may decrease milk production and should therefore also be avoided during breastfeeding. Bugleweed (Lycopus spp),[130] parsley (Petroselinum crispum) and sage (Salvia offivinalis)[111,121] are examples of herbs that result in decreased maternal milk production.

CONCLUSION

Herbal medicines have wide spread usage internationally and are the major health care modality in many ethnic groups. Even in Western societies, the usage of herbal medicines is steadily increasing. However, many of these herbal medicines are not accepted by the governing medical and pharmaceutical bodies such as the US Federal Drug Administration (FDA). There are good reasons for this. Natural medicines are currently not controlled in the same way as conventional medicines. To gain widespread acceptance by Western medicinal systems, herbal medicines must be held to the same standards as allopathic medicines. Commercial herbal preparations need standardisation of the active phytochemicals as well as those

Table 9 : Herbal drugs which should be avoided during lactation.

Common Name	Species Name	Medicinal Effect	Adverse Effect	Ref.
Aloe	various Aloe species including Aloe ferox Aloe barbadensis,	antiseptic, immune stimulator, anti-inflammatory, treatment of diabetes	can induce colic and diarrhoea in infants	12, 73, 111, 143, 144
Anise	*Pimpinella anisum*	relief of menstral cramps, carminative, insecticide	may induce hormonal effects in infants	131, 132
Black snakeroot	*Cimicifuga racemosa*	gynecological disorders, sore throats, kidney problems, depression	may cause stomach upset in infants estrogenic effects	136
Borage	*Borago officinalis*	metabolic and hormonal regulation, gynecological disorders, menopause symptoms	may cause liver toxicity in infants	121
Buckthorn	*Rhamnus catharticus*	purgative	affects uterine muscle tone	111
Bugleweed	Lycopus spp.	astringent, sedative, treatment of anxiety and palpitations	has a hormonal effect, may reduce lactation and milk volume	130
Cascara sagrado	*Rhamus purshiana*	laxative	can induce colic and diarrhoea in infants	52, 111
Coltsfoot	*Tussilago officinale*	cough suppressant, asthma and lung disorders	contains alkaloids, may cause liver damage in infants	111
Comfrey	*Symphytum officinale*	brocchial problems, arthritis, ulcers, burns, acne and other skin disorders	contains alkaloids, may cause liver damage in infants, causes blood clots	52, 121
Cork tree	*Phellodendron amurense*	anti-inflammatory, diarrhoea, antiseptic, stomach disorders	contains alkaloids, may affect the nervous system in infants	150
Dang gui	*Angelica sinensis*	treatment of gynecological disorders, fatigue, high blood pressure. Has analgesic, antispasmodic, antiinflammatory and sedative effects	may stimulate the nervous system, may cause light sensitivities	111
Elecampane	*Inula helenium*	tonic, stimulant, expectorant, antiseptic induces menstruation	causes gastrointestinal upsets in infants	111
Ephedra	*Ephedra sinica*	stimulant, weight loss, treatment of asthma, allergies, cold	stimulates the nervous system in infants	124
Wu zhu yu	*Evodia danielli*	treatment of headaches and digestive disorders, analgesic, antithelmintic, astringent, carminative, decongestant, diuretic, stimulant	contains alkaloids, may affect the nervous system	111
Fennel	*Foeniculum vulgare*	carminative, treatment of colic, digestive disorders, alleviate bloating	fennel essential oil is toxic, can cause convulsions and respiratory problems	111, 121
Fenugreek	*Trigonella foenum-graecum*	arthritis, induces lactation, treatment of diabetes	may cause allergic reactions in infants, causes colic and diarrhoea in babies, may cause hypoglycemia in nursing mothers	121
Garlic	*Allium sativum*	arteriosclerosis, hypertension, fever, hypercholesterolemia, infection	may taint milk flavour resulting in decreased ingestion by infants	111
Ginkgo	*Ginkgo biloba*	cardiovascilar disease, improves memory	inhibits platelet formation	124
Ginseng	several species of the genus Araliaceae	stress reduction, improves vitality	Estrogenic effects, may induce hormonal effects in infants	111, 121
Gold thread	Coptis spp.	general tonic, sedative	contains alkaloids, may affect the nervous system	111
Gravel root	*Eupatorium purpureum*	diuretic, stimulant, tonic, astringent, relaxant	Contains alkaloids, may cause liver toxicity	111

Kava kava	*Piper methysticum*	treatment ofanxiety, stress, muscular pain, insomnia	May affect nervous system and cause liver damage	124
Liquorice	*Glycyrrhiza glabra*	cough, peptic ulcer, treatment of arthritis and other auto-immune disorders	many cause hormonal effects in infants	124
Male fern	*Dryopteris filix-mas*	antithelmintic, vermifuge, astringent	induces nausea, vomiting and diarrhoea	111
Parsley	*Petroselinum crispum*	good source of vitamin c, treatment of asthma, anemia, obesity, rheumatism tooth ache, indigestion, intestinal parasites	may reduce maternal milk production	111, 121
Rauwolfia	*Rauwolfia serpentina*	antihypertensive, reduces blood pressure, sedative, hypnotic	may cause blood pressure changes in infants	151
Rhubarb	*Rheum officinale*	laxative, purgative, astringent, tonic, antipyretic, hemostatic	induces nausea, vomiting and diarrhoea in infants	111
Sage	*Salvia officinalis*	carminative, stimulant, diuretic, antispasmodic, expectorant, tonic, antiseptic, treatment of diarrhoea	may reduce maternal milk production reduces blood sugar levels	111, 121
Senna	Senna spp.	constipation	can induce colic and diarrhoea in infants	52
Sophora root	*Sophora japonica*	antiseptic, anti-inflammatory, diuretic, antispasmodic, emetic, emollient, febrifuge, hypotensive, purgative, tonic	contains alkaloids that affect the nervous system	147
Stillingia	*Stillingia sylvatica*	astringent, cathartic, diuretic, emetic	can induce colic and diarrhoea in infants	111
Tripterygium	*Tripterygium* spp.	treatment of autoimmune disorders including arthritis, systemis lupus, antitumour	powerful immunosuppressant effects	138
Wormwood	*Artemisia absinthium*	antiseptic, antithelminic, antispasmodic, carminative, febrifuge, narcotic, tonic, stimulant	induces vomiting, intestinal cramps and disturbances of the nervous system	111, 121
Wintergreen	*Gaultheria procumbens*	analgesic, astringent, carminative, diuretic, stimulant, antispasmodic, antiseptic, treatment of rheumatism	contains methyl salicylate which is counterindicated in infants and children	111

compounds responsible for counterindications, side effects and toxicities. Herbal medicines need more extensive research to provide a greater understanding of how they work and to allow a prediction of how to take herbal medicines safely. The industry needs to set guidelines regarding adulteration and contamination. Manufacturers providing ineffective, toxic or incorrectly labelled medicines are not only damaging the industry, they are also endangering the health and well being of their customers. Furthermore, education of physicians and herbal medicine practitioners is required to ensure that only combinations of herbal medicines and allopathic drugs which are safe and effective are used.

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CONFLICT OF INTEREST

The author declares no conflict of interest

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