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Drug Interactions Between Herbal and Prescription Medicines

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Abstract

Until reports of interactions between St John's wort and drugs such as digoxin, warfarin, protease inhibitors and oral contraceptives began to appear, very few herb-drug interactions were documented. These are now becoming more common, although still rare compared with drug-drug interactions. In the absence of hard data, potential interactions are being highlighted, and this review attempts to distinguish between the speculative and the proven. The subject is approached from a therapeutic point of view since in most cases the patient is already taking one or more prescription drugs, and the question is whether or not it is safe for a particular herb to be added to the regimen. Although many of the examples of herb-drug interactions are minor or theoretical at present, the fact remains that some are serious and life threatening, and these almost exclusively concern cyclosporin, anticoagulants, digoxin, antidepressants and protease inhibitors, taken with the herb St John's wort. Ginkgo and ginseng are implicated in a number of reports, but many of these are unsubstantiated. To date, the cardiovascular, central nervous and immune systems are the most common therapeutic categories cited in the literature and other than those, examples are very limited. Although many herbal drugs have good safety profiles, it must be borne in mind that herbal supplements are intended to be taken over an extended period of time, which provides the opportunity for enzyme induction and other mechanisms of interaction to take effect.

"The data on interactions are of widely varying quality and reliability. Sometimes they are no more than speculative and theoretical scaremongering guesswork, hallowed by repeated quotation until they become virtually set in stone" – Stockley.[1] These statements have been applied to all types of drug interaction reports, but are probably even more appropriate in the case of herbal medicines and prescription drugs. These will be referred to as 'herb-drug' interactions for convenience, although herbs are of course, in this context, drugs. Very few herb-drug interactions were documented until recently, when reports of interactions between St John's Wort and drugs such as digoxin, warfarin, protease inhibitors and oral contraceptives began to appear. They are now becoming more common, with the increasing use of complementary therapies and a greater awareness of the potential problem, although they are still rare compared with drug-drug interactions.

Several reviews on herb-drug interactions have been published recently[2-8] but in all cases these have been hindered by the lack of reliable documentary evidence. For example, Fugh-Berman and Ernst[3] identified 108 cases of suspected interaction by searching the major databases and contacting manufacturers, experts and herbal organisations, covering the period 1990–2000. This is a small proportion of drug interaction reports, and of these, they could only classify 13% as 'well-documented' and 18.5% as 'possible' interactions; the remainder were 'unevaluable'. With the extent of the problem still unknown, and in the absence of hard data, potential interactions are being highlighted instead.[9-13] This approach has both benefits and drawbacks. It acts as an alert to a potential interaction, and if the hypothesis is used properly the evidence can then be examined, and can exonerate as well as implicate the herb in an interaction. For example, Miller and Murray[10] state that "echinacea may interfere with immunosuppressive therapy", Barnes et al.[11] suggest that saw palmetto "may interfere with existing hormone therapy" and Ang-Lee et al.[12] state that valerian "could increase the sedative effects of anaesthetics". In contrast, when Fugh-Berman and Ernst[3] reviewed literature reports with the aim of assessing the quality of the clinical evidence, they found no reports of interactions between conventional treatments and echinacea, valerian or saw palmetto.

The Mayo clinic website (www.MayoClinic.com) provides a list of herbs and specifies drugs that

should not be taken concurrently, and is a useful site, particularly for consumers. However, to ensure that patients are well protected, the information provided on the website includes some potential, unproven and theoretical interactions, and is not referenced to the scientific literature. It is widely recognised that more research is urgently needed, and it is also extremely important that the identity and constitution of the herbal drug is known accurately, because of the possibility of substitution, contamination or other forms of adulteration.

Most articles on the subject of herb-drug interactions approach it from the point of view of the herb, and those prescription drugs that may interact with the herb. However, in most cases the emphasis is on the prescription drugs already being taken by the patient, and whether it is safe for a particular herb to be added to the regimen. In this review, therefore, drug interactions will be discussed according to drug therapeutic type, and a distinction made between those interactions for which evidence is available, and those that are unreliable or purely speculative. A very brief outline of mechanisms will be given so that a particular type of interaction can be put in context.

1. Mechanisms of Drug Interactions with Herbs

Many herbal products are treated as 'food supplements' for legal and regulatory purposes, although strictly speaking they do not fall into that category, and here they will be considered as medicines. Food intake – time, quantity and content – can certainly affect drug treatment and this subject has been well reviewed recently by Schmidt and Dalhoff.[2] There are some high profile food-drug interactions, particularly involving grapefruit juice, and drug absorption (and therefore bioavailability of the drug) seems to be the main parameter affected by the presence of food in the stomach. Similar principles will apply to herbs, which often contain similar compounds, albeit in much higher concentrations. Mechanisms of interactions are necessarily complex, and more than one may be involved. They are usually divided into pharmacokinetic and pharmacodynamic interactions, the former being processes involving absorption, distribution, metabolism and excretion, and the latter being those where the effects of one drug are affected by the presence of another, at the site of action (sometimes called pharmacological interactions), which are less predictable and more difficult to classify.

1.1 Pharmacokinetic Interactions Involving Herbs

Most interactions affecting absorption usually result in a reduction of the absorption of the drug, although increases in absorption can occur. Changes in intestinal pH will affect absorption, as will complexing mechanisms and drugs affecting gastrointestinal motility. Herbal drugs are more likely to inhibit absorption by forming complexes, for example with metal cations such as calcium, tannins and polyphenols in water extracts. In practice, this may not be significant – after all, tea, which contains all of these, is often used by patients to help swallow tablets, and does not appear to render many drugs inactive. Drug displacement from protein-bound forms, by concurrent drug administration, causes an increase in serum drug levels and therefore an increase in the therapeutic effect. This is very important in the case of antiepileptic agents for example, but no clinical cases have been reported for herbal drugs. Stockley[1] considers that this mechanism of interaction "has been grossly over-emphasised" because *in vitro* studies are not necessarily reflected by what happens in the body.

Drug metabolism is the most important mechanism so far reported for herbs, and the best known example is St John's wort. If the cytochrome P450 (CYP) enzymes which metabolise a particular drug are induced, they will obviously remove it from the circulation more rapidly, and if another drug is present which involves the same enzymes, that too will be metabolised faster. This is a very common mechanism, and applies to the way in which St John's wort may reduce the efficacy of the oral contraceptive pill or blood levels of warfarin, digoxin or theophylline.[14] The opposite may apply, where enzyme inhibition leads to increased drug levels, which can be an advantageous mechanism unless drug serum levels reach toxic levels. Changes in excretion will affect serum drug levels, and diuretics are often cited as causing this effect. However, herbal diuretics are very weak (compared with furosemide for example), and unlikely to cause any

problems. Most herbs do not change urinary pH to any large extent either; this is true for cranberry juice, which is used to treat cystitis. P-glycoprotein is a pump mechanism, which has a considerable effect on serum drug levels by blocking or facilitating entry into cells. This is an important mechanism and the subject of an increasing number of reports, including one that implicates St John's wort.[14]

1.2 Pharmacodynamic Interactions Involving Herbs

Additive, synergistic or antagonistic effects of combinations of drugs are possible with any type of drug, including herbals. Therefore herbal sedatives, anticoagulants, antihypertensives and others may possibly increase the effect of a concurrent conventional drug taken for the same purpose. Given that drug combinations such as these are routinely given in medicine (e.g. antihypertensives, cancer chemotherapies, and anti-HIV agents) and drugs tend to be much more potent than herbs, the clinical importance of this type of interaction has not yet been properly evaluated. Reports at present appear to be confined to the serotonergic syndrome reported for antidepressants taken with St John's wort. In order to predict this type of interaction, a certain amount of basic pharmacological knowledge is needed about both herb and drug, but unfortunately this is often lacking for the herb.

2. Problems Monitoring Herb-Drug Interactions

2.1 Definition of Herbal Medicines

The definition of herbal medicines has been loosely interpreted, as a complex mixture of substances extracted from plant sources. Although caffeine, tobacco and cannabis are not normally classified as such, they have been included for the following reasons: (i) caffeine is present in many stimulant herbal products, in the form of cola and guarana, and are often sold as tonics; (ii) guarana may be included in herbal products for energy, and referred to as a natural stimulant from the Amazon containing guaranine, to disguise the fact that guaranine is actually identical to caffeine;[15] and (iii) cannabis is not a herbal medicine, and although it will not be available without prescription, it is expected to be licensed soon for use in multiple sclerosis. Of course the illicit use of cannabis is very widespread indeed, and similarly with tobacco, not as a medicine but a widely used drug.

2.2 Retrieval of Herb-Drug Interaction Reports

Reports of herb-drug interactions are sparse (although they are increasing rapidly) for a number of reasons, and reliable figures of such interactions are not available.[16] Patients may not tell their practitioner that they have taken the herbal drug for fear of disapproval, or because they do not consider herbs to be 'drugs'. An interaction may not be recognised as such, and may only be reported if it is considered 'serious'. It is difficult to assess the incidence of herb-drug interactions, and even more difficult to assess the reliability of these reports, which often involve only one patient or is a theoretical case with no evidence, or an animal or *in vitro* experiment which is not relevant to a human clinical situation. Data are now accumulating, and there may soon be many such reports, although it is also possible that herb-drug interactions are either minor or tend to involve drugs already notorious for their potential to interact.

The following strategy was used initially to survey the literature: the literature databases Embase and Medline were accessed from their inception (1980 and 1966, respectively) until May 2003, using as key phrases 'herb-drug interaction', 'herbal medicine toxicity', and 'herbal pharmacokinetics'. The search term 'food-drug interaction' was also included, to identify any interactions in which herbal medicines may have been classified as food supplements. Standard references, particularly Stockley's Drug Interactions 6th edition[1] and others[10,11,15] were checked, and the references cited in these, and also the reviews identified by the computer searches[2-9,12] were consulted, to attempt to rectify any omissions by the abstracting services. Report reliability was difficult to assess; the scoring system described by Fugh-Berman and Ernst[3] which, although not validated, appeared to be the most useful. However, it proved to be impossible to apply this system to a large number of cases due to lack of information given in them, a factor noted by those

authors, who classified such reports as unevaluable. It was also not possible to tabulate observed interactions at this time without giving credence to too many unreliable reports.

2.3 Classification of Herb-Drug Interaction Reports

The evidence available for each report has been outlined where possible, and an attempt made to implement a broad classification using the following definitions:

- **Confirmed:** interactions that are backed up by data on a number of reports, a rechallenge of the co-administered drug resulting in a similar effect, or knowledge of the mechanism of action. Example: St John's wort (*Hypericum perforatum*) and hormonal contraceptives (see section 3.4.1).
- **Potential:** possible interactions with a sound theoretical basis and one or more reports already received. Example: dong quai (*Angelica sinensis* root) and warfarin (see section 3.1.1).
- **Theoretical:** with a more tenuous theoretical basis, and no clinical reports. This category is responsible for most of the 'theoretical scaremongering guesswork' described by Stockley.[1] Example: echinacea and immunosuppressants (see section 3.8).
- **Unlikely:** a report of an adverse event occurring when two drugs are taken concurrently or in an animal experiment, but where theoretical considerations mean an interaction is unlikely or not translatable into a human situation. Example: capsaicin cream with an ACE inhibitor (see section 3.1.4).
- **A single report:** exactly that; unevaluable. Example: ginkgo (*Ginkgo biloba*) and trazodone (see section 3.2.1).

3. Herb-Drug Interaction Reports

3.1 The Cardiovascular System

Patients receiving anticoagulant therapy are usually very cautious about concurrent drug use, although they may not inform the prescriber of their herbal medicine consumption, for reasons already mentioned. The majority of reports concern warfarin and the cardiac glycosides (mainly digoxin) which are known for their many interactions due to an inhibition of CYP enzymes. These drugs are potent, have a narrow therapeutic window and changes in serum levels can have serious consequences. Other interactions are known and will be outlined.

3.1.1 Warfarin

The main reports concern an enhancement of the effect of warfarin either by decreasing clearance and therefore increasing bioavailability, leading to an elevation of the International Normalized Ratio (INR) and prothrombin time (PT) with concurrent herbal use. At present no fatalities have been recorded, but this is probably due to the fact that these patients are closely monitored in the clinic and the dose of warfarin adjusted routinely. Notable interactions occur between warfarin and several herbs used in traditional Chinese medicine, such as dong quai,[17] dan shen (*Salvia miltiorrhiza*)[18] as well as garlic (*Allium sativum*) and ginkgo.[19]

Confirmed Interactions

St John's wort is a popular herbal medicine taken for mild to moderate depression. It has been shown to interact with a number of drugs, including warfarin, mainly due to an induction of CYP2C9. It caused a decrease in the anticoagulant effect of both warfarin (seven cases) and phenprocoumon (one case),[20] although paradoxically in another case, it caused an increase in anticoagulant effect in one patient taking phenprocoumon.[20] The UK Medicines and Healthcare products Regulatory Agency (MHRA) [formerly the Medicines Control Agency] has recommended that patients on warfarin should not take St John's wort and that those already doing so should stop, and adjust their dose of anticoagulant.[21]

Potential Interactions

Dong quai is used as a hormone regulator in women for disorders such as painful or suppressed menstruation and symptoms associated with menopause, although it is considered to be devoid of estrogenic activity itself.[15] Dong quai, together with warfarin, produced an increase in INR and PT in a single case report in one patient[17] and a pharmacodynamic (but not pharmacokinetic) interaction has also been documented for the same combination in rabbits.[22] Although dong quai is also used by traditional Chinese medicine practitioners for

cardiovascular indications, a study showed that it conferred no benefit to stroke patients.[4]

Haemorrhage has been reported in two patients taking a combination of warfarin with dan shen[18] (which decreases warfarin clearance). Although in these instances the patients were also taking other drugs (furosemide and digoxin in both cases), the interaction was ascribed to the dan shen component. A Chinese herbal formulation, kangen-karyu, which is a mixture containing dan shen, peony root, safflower, saussurea root, and cnidium and cyperus rhizomes, is traditionally used to treat hypertension and atherosclerosis, with proven clinical efficacy.[18] A desire by some patients in Japan to take a combination of kangen-karyu with warfarin led to an investigation of the pharmacokinetic interactions in mice, although these have not been documented in any clinical reports. This showed that kangen-karyu significantly suppressed the metabolism and elimination of warfarin, although serum binding and absorption were not affected.[18] The authors concluded that the combined use of these drugs may be therapeutically advantageous provided that coagulative status was checked regularly.

Theoretical Interactions and Single Reports

Garlic, a common supplement taken to improve cardiovascular health has been reported (rarely) to cause an increase in INR when taken with warfarin.[19] Ginkgo (taken to improve the circulation and hence cognitive function) and ginseng (a general tonic and adaptogen) have both been subjects of reports of possible interactions, although with no supporting data,[19] and Stockley concludes that there is no real substance of such reports.[1] In the case of ginseng, the combination resulted in a decrease in INR,[23] but the assessors of this report suggest that causality is difficult to prove.[24] The consumption of ginseng is more widespread among the elderly population, who are most likely to be taking warfarin, and these reports may be taken as an indication of a potential for interaction, rather than confirmed, in view of the fact that there have been reports of spontaneous bleeding in patients taking ginseng alone.[1]

Recently, a single report has been documented between a herb used in traditional Chinese medicine (Chinese wolfberry [*Lycium barbarum*]) and warfarin, leading to an increase in INR. The patient, a 61-year-old woman, was also taking digoxin, atenolol and fluvastatin.[25] Other single reports include the case of a woman on warfarin taking a herbal product containing boldo (*Peumus boldo*) together with a separate product containing fenugreek (*Trigonella foenum-graecum*). The patient's INR was elevated modestly but no undesirable reactions such as bleeding or bruising were observed.[26] Similarly, two patients taking the herbal remedy curbicin, for prostate enlargement (containing pumpkin seed, *Cucurbita pepo*, and saw palmetto, *Serenoa repens*) showed elevated INR values although only one was also taking warfarin.[27] Quinine, derived from cinchona bark, is occasionally found in herbal products as well as carbonated drinks. An interaction has been reported in two women receiving warfarin, and a man taking phenprocoumon, who were drinking large quantities of tonic water containing quinine. Stockley suggests that this is of little or no clinical significance.[1]

Many other items of food are used in concentrated form as health supplements, and several authors suggest a theoretical interaction between ginger (*Zingiber officinalis*) and warfarin.[19,23] Again this is unsupported by clinical evidence. Other unsubstantiated claims are that psyllium seed (*Plantago psyllium*) and ispaghula husk (*Plantago ovata*), taken for the fibre content as a bulk laxative, may inhibit the absorption of warfarin, but a small study in six healthy individuals showed no effect on either the absorption or anticoagulant effect.[28] Cases have been described where a high intake of mango fruit together with warfarin caused an elevation in INR,[29] but the interaction is not important and patients need not avoid eating mangoes.

It is well known that dietary vitamin K, contained in many green vegetables, can antagonise warfarin (it is used as an antidote for warfarin overdose). This is suggested as a factor in the case of a patient on warfarin who developed an elevated INR when consuming large volumes of green tea (2–4L daily for a week),[30] although this is an unlikely interaction, as it would be more logical to assume that the vitamin K would decrease the INR. A more likely scenario is that the polyphenols in the tea (given the large amount ingested) may have inhibited the absorption of the warfarin in some way. Possible interactions

for patients taking warfarin with, for example, feverfew (*Tanacetum parthenium*), for migraine prophylaxis, and ginkgo, as an aid to circulation, have been postulated by several authors.[10,11] No clinical interactions have been reported to date but it would probably be wise to avoid these combinations. Similarly, plants containing salicylates, such as meadowsweet (*Filipendula ulmaria*) and willow bark (*Salix* spp.)[15] should be avoided with anticoagulants. Closer monitoring of INR would probably be advisable for these patients also taking herbal medicines, and this may also give information as to the extent of the problem.

Potential Additive Effects

Various herbs are used in both traditional Chinese medicine and traditional herbal medicines for cardiovascular problems. Natural anticoagulants include coumarin derivatives, contained, for example, in sweet melilot (*Melilotus officinalis*), tonka beans (*Dipteryx odoratum*) and sweet woodruff (*Galium odoratum*),[15] and obviously these may have additive effects with warfarin. A case study in a woman taking a herbal tea containing all of these plants, together with warfarin, showed an abnormal menstrual bleeding and a reduction in clotting factors, but the PT returned to normal after she was given parenteral vitamin K.[1] Naturally-occurring coumarins are only weakly anticoagulant, but if the plant material is not stored properly dicoumarol may be formed by microbial transformation, and this compound is much more potent. A list of herbs with varying cardiovascular effects can be found in several texts,[4,7,10,11] but it must be borne in mind that most of these have not yet been associated with any interaction reports.

A Case of Deliberate Adulteration

A formulation called PC-SES, taken for prostate cancer, contains the Chinese herb, baical skullcap (*Scutellaria baicalensis*), which is reputed to be an anticoagulant. This product caused a massive increase in PT and associated clinical symptoms in a patient, although not in conjunction with any other anticoagulant therapy.[31] On analysis, this product was found to actually contain warfarin, and has now been withdrawn from sale.[32] This example serves as an illustration of a so-called herbal product, which is not what it appears to be, and how a particular herb may be implicated in toxicity reports with no foundation in truth.

3.1.2 Digoxin

The use of cardiac glycosides such as digoxin is decreasing because of the availability of safer drugs for heart failure, but digoxin is still widely used and poses a potential problem for patients wanting to take herbal remedies.

It has been confirmed that the excessive use of laxatives, including the herbal drugs senna (leaves and pods of *Cassia senna* and other *Cassia* spp.) and cascara (*Rhamnus purshiana*), depletes blood electrolyte levels, particularly potassium, which contributes to the toxicity of digoxin.[10,11]

There is clinical evidence that blood levels of digoxin are reduced by the concurrent administration of St John's wort,[11,14] although, to date, no therapeutic interactions between St John's wort and digoxin have been reported. If a patient insists on taking both he/she should be closely monitored. However, the UK Committee for the Safety of Medicines (CSM) recommends that St John's wort and digoxin should not be taken together.[11]

An elderly patient taking Siberian ginseng (*Eleutherococcus senticosus*) with digoxin was found to have grossly elevated digoxin levels, although no symptoms of toxicity were found.[33] Although not everyone with high digoxin levels necessarily has symptoms, another reason for this apparent contradiction might lie in the assay procedure for blood digoxin levels, which is a serum immunoassay method. Both the active constituents have a steroidal chemical structure, which could interfere with the results of the assay.[1] However, it has been argued that the chemical structure of the compounds present in Siberian ginseng are not very similar to that of digoxin, and a more likely explanation is that the ginseng had been adulterated with *Periplocia sepium*, the constituents of which are closer in structure.[33] The substitution of Siberian ginseng has been responsible for other adverse events ascribed to the herb, such as androgenicity.[34]

3.1.3 Calcium Channel Antagonists

A theoretical interaction has been reported with nicardipine and ginkgo. Ginkgo extract fed daily to rats (0.5% w/w of the diet) was found to attenuate the hypotensive response of nicardipine, by a mech-

anism involving the induction of CYP3A2 and other liver metabolising enzymes.[35] The level of ginkgo extract fed to the animals was much higher than would ever be when taken as a human supplement (to put in perspective: daily consumption of 1kg food would contain an intake of 5g extract, whereas the recommended dose is 120mg). No clinical interactions have yet been reported, but caution should be taken with long-term, high dose ginkgo extract supplementation, and those calcium channel antagonists which are metabolised by the same enzymes, i.e. nifedipine and diltiazem, as well as nicardipine.

3.1.4 ACE Inhibitors

ACE inhibitors are used for hypertension, and in the treatment of heart failure. In general, when taken with herbal medicines they appear to have a good safety profile, although a report has been made of interactions of garlic with lisinopril, by a medical practitioner. He described his own symptoms of hypotension and fainting, which were restored to normal on cessation of the garlic.[36]

A woman taking an unnamed ACE inhibitor experienced a cough after applying capsaicin cream topically as an analgesic.[37] Capsaicin is the pungent ingredient in chilli peppers (*Capsicum* spp.), and is included in several herbal products for coughs and colds due to its expectorant and 'warming' effect. It is not known how much, if any, capsaicin was systemically absorbed. ACE inhibitors are known to produce cough as an adverse effect and if this is indeed an interaction, which is not proven, it is unlikely to be clinically significant.

3.1.5 Antiplatelet Drugs

Antiplatelet drugs do not seem to interact with most herbal medicines, although there is the potential for an additive effect with, for example, herbs containing salicylates, or ginseng or ginkgo, which are known to have antiplatelet activity.[11]

Conversely, an elderly man already taking aspirin (acetylsalicylic acid) after coronary by-pass surgery, developed spontaneous bleeding from the iris into the anterior chamber of the eye and blurred vision when he started taking ginkgo. The bleeding stopped after cessation of ginkgo.[38] Ginkgo contains ginkgolides, which are unique terpene lactones with specific platelet-activating factor antagonist activity, and has been associated with spontaneous bleeding when given alone without concurrent medications. For example, a woman who had been taking warfarin for several years also experienced intracerebral haemorrhage after initiating ginkgo.[39] Aspirin is also associated with similar reports.[40]

Theoretically, feverfew, ginger, kava (kavain, *Piper methysticum* - now largely withdrawn from sale because of hepatotoxicity) and dong quai, which have antiplatelet effects *in vitro*, may affect concurrent antiplatelet therapy,[10,11] but there are no reports published of clinical interactions. One further example is that caffeine, present in cola and guarana tonics (*Cola nitida* and *Paullinia cupana*, respectively) as well as tea and coffee, antagonises the haemodynamic response to dipyridamole testing, which may or may not be clinically relevant.[1]

3.2 The Central Nervous System

3.2.1 Antidepressants

Confirmed Interactions

Mild depression may be self-treated by patients unwilling to consult a doctor for a condition perceived to carry a stigma, and if so, a popular herb used to treat this condition is St John's wort. If there are no concurrent prescription drugs, St John's wort has a fairly good safety profile, but of course the patient may be on other non-depression-related medication. It is also common for patients to add this herb to an existing antidepressant drug regimen, either to boost the effect or with a view to replacing it with something natural on their own initiative, and without consultation. This is where interactions can arise, and have been recorded. The most common is a potentiation of serotonergic effects with concomitant specific serotonin uptake inhibitors (SSRIs) such as sertraline, paroxetine and fluoxetine. In addition to duplicating effects, it is also due to the inhibition of CYP2C9, CYP2D6 and CYP3A4 by this class of drugs. It is important to remember that the long half-life of fluoxetine, as well as the activity of its main metabolite norfluoxetine against CYP3A4, means the potential for interaction remains for several weeks after discontinuation.[41] St John's wort also inhibits CYP3A4 (as well as CYP1CA2, CYP2CP,[42] and it also affects P-glycoprotein) which explains at least in part the mecha-

nism for this. A report of mania associated with concomitant administration of sertraline and St John's wort was considered to be serious.[43]

Monoamine oxidase inhibitors (MAOIs) interact with reserpine (a rauwolfia alkaloid) in an interesting way, in that it depends on the order in which the drugs are given. Stockley[1] explains this interaction as follows: the rauwolfia alkaloids cause a release and subsequent depletion of noradrenaline stores, reducing the transmission of adrenergic nerve endings, which leads to hypotension and depression. In fact, an animal model of experimental depression induced by reserpine is used to test new antidepressant compounds. If the patient is already taking an MAOI, and rauwolfia is added, there may be a sudden release of accumulated noradrenaline (norepinephrine) and serotonin, resulting in excessive stimulation of the receptors, manifesting as gross central excitation and hypertension. It is referred to as reserpine-reversal and has been reported for phenelzine [44] and nialamide.[45] This reaction is obviously undesirable, and if it is absolutely necessary to give both drugs, the MAOI should be given after the reserpine or rauwolfia.

Theoretical Interactions and Single Reports

Two reports of theoretical interactions between an MAOI (phenelzine) and ginseng (*Panax ginseng*) have been noted.[46] In both cases, insomnia and headache were seen. Ginseng is known to have stimulant effects[11,15] but the mechanism of this interaction is not known, and MAOIs are known to produce insomnia and headache as adverse effects, even in the absence of other drugs.

An isolated report of mania, considered to be due to fluoxetine interacting with cannabis has been recorded.[47] This was attributed to the tetrahydrocannabinol (THC) content, which is also an inhibitor of serotonin uptake. Although cannabis is not yet used as a medicine, it is widely used illicitly. Also THC is already licensed for medical use in some countries (as dronabinol) and preparations of the herb are likely to follow suit, so vigilance is required. This single report from 1991 has not been repeated since, but users of an illicit drug would not necessarily report such problems, which may explain their absence in the literature.

An interaction between atropine and amitriptyline resulting in mydriasis has been reported in a neonate,[48] but this is probably a rare combination and of little clinical importance with regard to herbal medicines. Although atropine is a natural product, from *Atropa belladonna,* it is rarely used in its herbal form unless by a qualified medical herbalist, who will be aware of the toxicity of the herb, and most unlikely to use it in babies. Tricyclic antidepressants have been the subject of occasional interaction reports but do not seem to pose a major problem with common herbal remedies.

Trazodone is used in depression where sedation is required, particularly in the elderly. An interaction resulting in coma was suspected in an Alzheimer's patient taking a low dose of trazodone with ginkgo, but this is unproven.[49]

Potential Additive Effects

The root of rauwolfia, which contains reserpine and other alkaloids, was formerly used as a treatment for psychoses including schizophrenia, and hypertension. It is occasionally found in imported medicines from Asia, where it is still used for those purposes and as a sedative. Rauwolfia itself can cause depression so it is usually avoided in patients with, or prone to, depression. However, it has been shown that when taken in conjunction with the tricyclic antidepressants, imipramine and desipramine, there has been successful treatment of some forms of resistant depression in a few cases.[50] This has only been attempted in a well controlled clinical situation.

3.2.2 Antipsychotics

Potential Interactions

Several cases have documented lower blood levels of fluphenazine and chlorpromazine in patients who were heavy smokers (of both tobacco and cannabis) compared with that of non-smokers.[51-53] Generally, this is thought to be due to enzyme induction as a result of smoking, which is well known, and therefore leads to an increased metabolism of the antipsychotic drug. A comparative study of 403 patients on chlorpromazine found that drowsiness (an adverse effect and an indication of blood levels) was decreased according to the level of smoking,[51] and a patient who gave up smoking experienced increased sedation and higher blood

levels of the same drug.[52] When cannabis was involved in addition to tobacco, the effect was even greater, according to a study of 31 patients on chlorpromazine.[54] A similar effect was seen in patients taking fluphenazine, and clearance of the drug was much higher in the smokers.[53] No change in behaviour was seen. So, as far as clinical management is concerned, it may be necessary to use larger doses in smokers, and also to be alert to the possibility of reducing the dose if the patient stops smoking.

Seizures were reported in two patients taking fluphenazine with evening primrose oil (which contains gamolenic acid) and in one patient taking placebo with evening primrose oil in a study of 23 patients with schizophrenia.[55] Conversely, another, crossover study in 48 patients, the majority of whom had schizophrenia, recorded no seizures when patients were given a combination of phenothiazines and evening primrose oil.[56] No reports have been made of seizures in patients receiving evening primrose oil who are not taking phenothiazines, (which are known to be epileptogenic themselves), although another study in hospitalised patients with schizophrenia found that evening primrose oil exacerbated the disease, and also produced EEG evidence of temporal lobe epilepsy.[57] The situation is obviously unclear and Stockley[1] considers the interaction to be not well established, but suggests monitoring if phenothiazines are taken together with evening primrose oil, as a precaution.

Theoretical Interactions

A study of the pharmacokinetics of clozapine in healthy volunteers concluded that the ingestion of caffeine 400–1000 mg/day inhibits the metabolism of clozapine to an extent that may be clinically significant.[58] No clinical reports have been documented and clozapine levels are monitored regularly in all patients.

Many herbal preparations contain polyphenolics and tannins, and a single report of two cases of schizophrenia being exacerbated by increased consumption of tea and coffee has been discussed.[1] The original author of this case report considered it to be an interaction with caffeine[59] but after studies showed that many phenothiazines complex with tannins and precipitate out *in vitro*, it was decided that this was probably the mechanism involved. Further evidence for this theory was obtained when it was found that, in rats, tea abolished the cataleptic effects of chlorpromazine, and was unrelated to the caffeine content,[60] but a clinical study of 16 patients with mental health problems showed that their intake of tea and coffee had no effect on either blood levels of antipsychotic drugs or their behaviour.[61] Since in the acid conditions of the stomach, the tannin-drug complex would dissociate, it is likely that this physico-chemical interaction is of no clinical significance – and the original report remains unexplained.

3.2.3 Lithium

Lithium is the most commonly used drug in bipolar disorder and blood levels must be checked regularly to avoid toxicity. Any substance which can affect this (and many do, as does food) have a potential for interaction. Patients taking bulk fibre preparations containing ispaghula or psyllium were found to have lower blood levels of lithium. The mechanism of action is not known, but either absorption of lithium was reduced, or perhaps the (unnamed) preparations contained high levels of sodium (in the form of bicarbonate) to aid dispersal in water before ingestion.[62]

A herbal diuretic was been implicated in the induction of lithium toxicity in a patient taking a proprietary mixture containing juniper, buchu, horsetail, corn silk, bearberry, parsley, bromelain and paprika.[63] Herbal diuretics are weak in comparison to modern drugs and it is unclear whether this theoretical interaction was due to diuresis or some other effect such as enzyme inhibition. The patient had been actually taking it for slimming, and in these cases people often use much higher doses than would normally be expected.

3.2.4 Levodopa

It has been observed that the effect of levodopa was reduced by the administration of reserpine (a rauwolfia alkaloid).[1] Since reserpine depletes neurotransmitter release (as explained in section 3.2.1), rauwolfia should not be taken by patients receiving levodopa.

3.2.5 Acetylcholine Receptor Antagonists

A confirmed interaction has been reported with betel (Areca) nut and procyclidine. Procyclidine is often used to control the extrapyramidal (parkin-

sonian) adverse effects of antipsychotics. It has been reported that in an Indian patient on depot fluphenazine, whose mild parkinsonian tremor was controlled by procyclidine, experienced severe rigidity and jaw tremor when he started chewing betel nut.[64] When he stopped chewing the nuts, these adverse effects disappeared. A similar effect was found in a patient taking flupenthixol.[64] Betel nut is sometimes used as a herbal medicine, but is much more widely used as a social and recreational stimulant. This interaction seems to be established and clinically significant, and patients on such drugs should avoid chewing betel nut (found in pre-prepared 'pan masala' also). It is fairly easy to check whether a patient has been chewing betel nut as it stains the mouth red. Betel nut contains arecoline and arecaidine among other alkaloids, and high consumption is associated with oral carcinoma, so it is best avoided in any case.[15]

3.2.6 Antiepileptic Drugs

Potential Interactions

Evening primrose oil and borage oil are taken for conditions such as premenstrual syndrome and eczema. They contain gamolenic acid, which reportedly lowers the seizure threshold, and it is often recommended that patients avoid it.[10,11] There are no substantiated reports of potential interactions with concurrent antiepileptic drugs, although as mentioned in section 3.2.2, seizures have been reported in two patients taking fluphenazine with evening primrose oil (and one taking the placebo), indicating the possible risks of inducing seizures.[56]

Theoretical and Unlikely Interactions

St John's wort is known to interact with some medicines by nature of its inhibition of cytochrome enzymes. However, it does not interfere with carbamazepine clearance[65] and no clinical reports are available to suggest that is unsafe, although caution is, as always, recommended in epileptic patients because maintaining therapeutic blood levels of antiepileptic drugs is of critical importance.[40]

Spinella[66] has drawn attention to the theoretical possibility for some herbal medicines to interact with antiepileptic drugs, although there are no recorded instances. Sedatives such as valerian (*Valeriana* spp.), passionflower (*Passiflora* spp.) and kava may theoretically potentiate medication for epilepsy, since they have shown to possess anti-seizure activity in animal experiments. Valerian contains compounds that inhibit the breakdown of GABA and enhance benzodiazepine binding[67] which could potentiate, for example, the effects of carbamazepine. Valerian also reduces the anxiogenic effects of diazepam withdrawal,[68] which may prove a useful therapeutic effect. Passionflower contains chrysin, a flavonoid, which acts as a partial agonist at the benzodiazepine receptor, and in mice this compound shows anti-seizure effects which are prevented by prior injection of a benzodiazepine antagonist.[69] Many herbs (and foods) contain flavonoids, and their activity is weak compared with the synthetic antiepileptics, and so far there are no reports of clinical interactions. Therefore the most likely source of problems is if patients attempt to replace their current medication with an unproven herbal product, thus precipitating seizures.

Stimulants containing caffeine (e.g. guarana, cola) may exacerbate seizures by lowering a patient's seizure threshold.[70] Caffeine also has also been shown to exacerbate seizures in animals.[70] However, since epileptic patients are unlikely to be consuming tea and coffee in greater quantities as the rest of the population, any potential problem, if at all, will probably only arise from products containing high levels of caffeine.

Essential (volatile) oils are present in many herbs and spices, and contain some known epileptogenic compounds (cineole and camphor in particular, and also fenchone).[71] The levels of these found in food and herbs are unlikely to cause major problems as they are not particularly important as constituents from a flavouring point of view. However, in the case of aromatherapy, it is possible that rosemary, sage, hyssop and fennel oils could be absorbed through the skin and should be avoided in epileptic patients as a precaution.[72] A report of three patients who experienced tonic-clonic seizures after using essential oils transdermally and orally, and the absence of these after discontinuation of the oils, confirms this possibility.[71] It should be noted that these patients did not have prior history of epilepsy, nor were they taking any other medication.

3.3 Pain and Inflammation

3.3.1 Salicylates in Herbs and Prescription Medicines

Salicylates are found in several plant medicines, such as willow bark (*Salix* spp.) and meadowsweet (*Filipendula ulmaria*) but when they naturally occur in plants they are chemically bound (for instance, in the form of glycosides) and appear to have a much lower propensity to cause gastrointestinal bleeding than, for example, aspirin.[15] Thrombolytics and antiplatelet agents are considered to interact with salicylates,[13] although currently no recommendations regarding dose adjustment can be made,[73] and by extrapolation, salicylate-containing herbs should probably be avoided, although no adverse reports have been made. A similar situation arises with ACE inhibitors and aspirin, but reports are conflicting and it is very common for patients to be taking both types of medicine concurrently,[74] so the interaction is probably not important in practice.

3.3.2 Other Unconfirmed Reports

Tamarind, an Asian fruit used as a flavour ingredient in cooking, and also as an Ayurvedic medicine, markedly increased the absorption of a single dose of aspirin 600mg in six healthy individuals.[75] The authors concluded that it could result in an increase in toxicity if large doses of salicylates are ingested. This may or may not apply to other salicylates and the significance of this interaction, if any, is not known with regard to herbal medicines.

A report of excessive bleeding by a patient taking rofecoxib with ginkgo was reported,[76] but the interaction was not confirmed and is probably not important.

Kakkonto is a Chinese herbal medicine containing liquorice, peony root, ephedra, ginger and other herbs, which in high doses in animal tests caused an increase in paracetamol (acetaminophen) levels.[77] However, in two separate studies in humans,[77] no effect was seen, even at doses of 5g. The interaction thus remains unconfirmed but is probably not significant.[77]

3.4 Sex Hormones

3.4.1 Confirmed Interactions

A number of reports have now been received concerning interactions between St John's wort and the contraceptive pill, which can lead to contraceptive failure.[14] Breakthrough bleeding has been reported, although this is a fairly common occurrence associated with many other factors, particularly missed doses.[14] While pregnancies have occurred with concurrent use of St John's wort and the contraceptive pill, they have also occurred with other drugs administered concurrently with the pill, as well as the pill alone. Definite causality of St John's wort affecting the efficacy of the contraceptive pill has not been established, although there are good reasons to suspect that it is a true pharmacokinetic interaction due to enzyme induction by St John's wort and an increase in the expression of P-glycoprotein, leading to lower drug levels, including that of the oral hormonal contraceptive pill.[78]

Two cases of failure of emergency hormonal contraception have also been reported when administered with St John's wort (although emergency hormonal contraception is not 100% effective even without St John's wort) and it is recommended that if patients are already taking St John's wort then an increase in the dose of emergency hormonal contraception should be considered.[1,14]

The number of cases of contraceptive failure is still fairly small, and the incidence of concomitant use of the pill and St John's wort is not known, so the actual risk cannot yet be assessed.[79] Current advice from the FDA in the US and the MHRA in the UK, is that concurrent use should be avoided.[21] If patients are already taking these medications concurrently, then St John's wort should be discontinued or additional contraceptive measures taken.

3.4.2 Theoretical and Unlikely Interactions

Tamoxifen is an estrogen antagonist widely used in the treatment and prevention of breast cancer. It was suggested in a letter to the *Australian Medical Journal*[80] that some herbal medicines that are used as either 'hormone regulators' or as a form of natural hormone replacement therapy (HRT) may directly stimulate breast cancer growth or oppose the actions of competitive estrogen antagonists, including tamoxifen. This raises questions about the mechan-

isms of action of these herbs, which is often not known, and in many instances, hormonal effects have not been conclusively demonstrated. Those mentioned included dong quai (*Angelica sinensis*), chasteberry (*Vitex agnus castus*) and black cohosh (*Cimicifuga racemosa*); however, generally these are not considered to have estrogenic properties.[15] On the other hand, herbs such as red clover (*Trifolium pratense*) and soya (*Glycine max*) contain estrogenic isoflavonoids; however, a high consumption of these as part of the diet is associated with a lower incidence of breast cancer. This paradox is thought to be a result of the isoflavones binding to estrogen receptors and acting as HRT agents, but by doing so they prevent the binding of the more potent endogenous estrogens, thus also acting as anti-estrogens. This is largely speculative at present, but since tamoxifen is a proven and highly effective drug in the management of breast cancer, it would pose unnecessary risks to combine its use with 'hormonally active' herbal remedies in the absence of more data.

A psychotic episode was reported in a young man taking testosterone after an orchidectomy, who was also given sertraline for depression and continued to take St John's wort against medical advice.[43] A manic episode ensued, involving elation, overspending on a car, arguments with his wife, and culminating in arrest by the police for stealing fuel for the car. Grandiose delusions followed, (in that he expected to be rescued by a team of soldiers and his father would visit in a private aeroplane) and the patient was sectioned under the 1983 Mental Health Act. The testosterone is probably unconnected to the episode and it is more likely to be an interaction between St John's wort with sertraline.

3.5 Diabetes Mellitus

3.5.1 Theoretical and Unlikely Interactions

An experiment in rats showed that an extract of *Angelica dahurica* (which contains furanocoumarins and is widely used in traditional Chinese medicine), delayed the elimination of tolbutamide *in vivo*.[81] It was attributed to the inhibition of CYP2C enzyme, but the extract also inhibits CYP3A and CYP2D1 and this would apply to other drugs metabolised by these routes.[81] No clinical reports have yet been made.

Miller and Murray[10] have suggested that the potential for interactions exists between insulin and oral hypoglycaemics and stimulant herbs, such as ma huang (*Ephedra sinica*), and also caffeine-containing products such as cola and guarana. This is because stimulants tend to elevate blood glucose and may therefore interfere with diabetic control. It is a theoretical possibility, and no cases have yet been recorded.

Aspirin and other salicylates have been known for over 100 years to cause hypoglycaemia in large doses. However, the amount of salicylates found in herbal drugs is unlikely to affect diabetic control.

3.5.2 Potential Additive Effects

The fruit of karela (*Momordica charantia*, or bitter gourd) is a vegetable eaten widely in tropical regions of Asia, the West Indies and Africa. The leaf is also available as a form of 'bush tea', known as 'cerassie' in the Caribbean. All parts of the plant are used as a treatment for type 2 diabetes mellitus in Ayurvedic and other forms of traditional medicine, and consumption leads to hypoglycaemia. This may affect diabetic control when taken alone, and all hypoglycaemic agents tend to have additive effects when taken in combination. A recent report showed that a patient who was poorly controlled when taking chlorpropamide alone, experienced much better diabetic control after ingesting karela with chlorpropamide.[82]

3.6 Antibacterials

An unlikely interaction between ciprofloxacin and fennel (*Foeniculum vulgare*) has been postulated after experiments in rats showed that lower blood concentrations of the antibacterial were found with concurrent administration of fennel extract.[83] The authors suggest that if this combination is taken clinically, then an adequate dose of ciprofloxacin be taken. However, the dose of fennel used (2 g/kg) in the animal experiment would translate to be over 100g of herb in humans, which is unlikely. Additionally, the study found that none of the organic components of fennel seemed to interact, and the most likely explanation was chelation in the stomach by metal cations found in the extract,[83] conse-

quently, this interaction (if such it is) is probably unimportant.

Khat (*Catha edulis*) is a mildly stimulant herb chewed as a social drug (in the manner of tea and coffee) in Africa and the Middle East, particularly in Yemen, and by the same ethnic populations in other parts of the world. It is occasionally used as a medicine, and has been shown to reduce the absorption of ampicillin, and to a lesser extent, amoxicillin, in a study of eight healthy Yemeni volunteers.[84] It is thought that this theoretical interaction was possibly due to formation of a tannin-antibiotic complex in the stomach.

A small decrease in the absorption of penicillin V was observed with concurrent oral administration with guar gum, in a study of ten individuals.[85] Since guar is taken to deliberately reduce absorption from the stomach (in diabetic patients, to avoid sudden peaks in glucose levels) this is not surprising and probably not clinically significant, especially in view of the fact that oral penicillin V should always be taken on an empty stomach.

3.7 Antiviral Drugs

Indinavir, a protease inhibitor used to treat HIV infection, is metabolised by CYP3A4, as is many other drugs – and the herb St John's wort. The FDA in the US and the CSM in the UK have warned about the possibility of an interaction between indinavir and St John's wort leading to lower blood levels of the antiviral.[21] This has been confirmed in a study using healthy individuals.[86] Although no clinical reports have yet been found, it is certainly possible that HIV-positive people would (or already do) take St John's wort because of its antidepressant properties. Lowered blood levels of indinavir could result in serious treatment failure, therefore St John's wort should be avoided by all patients on indinavir, other anti-retrovirals and also any drugs metabolised by the same enzyme.

3.8 Immunosuppressants

Cyclosporin is an important immunosuppressant used after organ transplant. Confirmed, serious interactions with St John's wort have been documented, including graft rejection in kidney, liver and heart transplant patients, and lowered blood levels of cyclosporin with concomitant administration were found.[87-89] In some cases blood levels of cyclosporin were well below therapeutic levels, and had dropped by an average of 49%. Both drugs are metabolised via CYP3A4, and as this can have serious consequences St John's wort should not be taken at the same time as cyclosporin.

A 54-year-old kidney transplant patient taking cyclosporin, in combination with azathioprine, prednisone, diltiazem and nifedipine, experienced a large increase (up to 8-fold) in cyclosporin blood levels. After investigation, it transpired that 2 weeks previously he had started drinking a tea containing *Geum chiloense*, a herb reputed to enhance virility. Blood levels returned to normal on cessation of this herb, but the mechanism of action was not determined.[90]

Glycyrrhizin, found in liquorice (*Glycyrrhiza glabra*), was found to reduce the clearance of prednisolone in healthy individuals.[91] It was considered to be due to inhibition of the metabolism of prednisolone, and the authors concluded that this interaction may have clinical benefits provided that toxic serum levels are not reached.[91]

Echinacea is taken as an immune stimulant, so there would be little point in taking it with an immunosuppressant. Nevertheless, a potential for interaction exists and it should probably be avoided. No clinical interactions have been reported.

3.9 Cancer Therapies

There is a potential for interactions between herbal remedies and cancer therapies, which has been discussed by Block and Gyllenhaal,[92] because of the effects of some herbs (particularly St John's wort) on drug metabolising enzymes. However, no actual herb-drug interactions have yet been reported clinically during cancer treatment. On the other hand, a potentially useful interaction has been described by Menéendez et al. who found that gamolenic acid, found in evening primrose and starflower (borage) seed oils, potentiated the *in vitro* cytotoxicity of paclitaxel and vinorelbine in human breast cancer cell lines. The authors suggest a role for some unsaturated fatty acids as modulators of tumour cell chemosensitivity.[93]

3.10 Miscellaneous Interactions

Diminished blood levels of theophylline (used in respiratory conditions) were found in a patient also taking St John's wort.[13] Although this patient was also taking many other drugs, her serum levels of theophylline returned to normal on cessation of St John's wort, and it was considered to be an interaction caused by induction of CYP enzymes.

Piperine is a constituent of black pepper and other species (e.g. *Piper nigrum, Piper longum*), which are a component of many Ayurvedic formulations, including trikatu. Piperine increases the bioavailability of many drugs and a number of cases have been documented.[94] The significance is not known, and no clinical reports have yet been made, but a regular, high dietary level of pepper (or ingestion of an Ayurvedic product containing it) may increase blood levels of other drugs such as phenytoin, propranolol and theophylline, and caution should be taken.

A case of myocardial infarction was reported in a patient taking sildenafil for erectile dysfunction and then smoking cannabis.[95] Although this was considered to be an interaction, serious cardiovascular events are listed as adverse effects in the general prescribing data for sildenafil.[96]

Some herbal medicines, including ma huang, yohimbe (*Pausinystalia yohimbe*) and liquorice can raise blood pressure even when taken alone.[15] Ma huang is taken as a slimming aid, decongestant and for asthma, and it has been abused as a stimulant in high doses. It contains the sympathomimetic alkaloid ephedrine, which can increase heart rate and peripheral vascular resistance. Liquorice is an ingredient of many traditional Chinese medicine preparations for a multitude of indications, especially stomach disorders, and excessive consumption is associated with pseudo-aldosteronism.[15] Yohimbe bark, which contains yohimbine, a presynaptic α_2-adrenoceptor antagonist (and possibly a MAOI), is sometimes used to treat erectile dysfunction. The problems posed by these herbal medicines in hypertensive patients have been reviewed by Valli and Giardiana[4] and Mansoor.[7]

3.11 Herbs and Surgery

Patients undergoing surgery may be taking herbal medicines without informing the anaesthetist, surgeon or physician, and this practice may have an impact on the peri-operative care of these patients. A hospital study of patients attending pre-anaesthetic evaluations in the US found that over half of the patients were taking some form of supplement, mainly vitamins but also herbal medicines.[97] The most common of these was garlic, followed by ginkgo, St John's wort, ma huang, echinacea, anthraquinone laxative drugs and liquorice. Some of these may well have the potential for interaction with drugs used during surgery, and it was recommended that a history of herbal supplements by the patient be taken. This would be helpful in determining whether or not interactions occur, if they are of clinical significance, and enable reliable advice to be given rather than suggesting that all supplements be avoided.

The effect of herbal medicines on the response to anaesthetics has not been evaluated, and consequently the American Society of Anaesthesiologists has recommended that all herbal medications be stopped 2–3 weeks prior to an elective surgical procedure.[98] Stringent recommendations were made recently regarding the precautions that should be taken, such as discontinuing ginkgo, ginseng and garlic because of the possibility that they may increase bleeding.[99] Since low-dose aspirin taken as an antiplatelet drug to prevent myocardial infarction is not contraindicated before surgery, it is not clear whether herbs would actually pose any risk. St John's wort is quite reasonably contraindicated for its potential to interact with other drugs, as is ma huang because it can increase blood pressure and heart rate. Furthermore, it has even been suggested that echinacea should be discontinued as soon as possible prior to surgery, because it may cause poor wound healing.[12] The rationale for this is not clear and there is no evidence that it inhibits healing. Traditional Chinese medicines have also been identified as potentially interacting with anaesthetics[100] and it was suggested that the anaesthetist be informed of any concurrent usage. Unfortunately this information is rarely available and an informed deci-

sion about the safety of such combinations cannot be made.

4. Conclusions

It is apparent that herb-drug interactions may be grossly under-reported for various reasons. Although many of the examples cited in this paper are unproven or purely speculative, the fact remains that some are serious and indeed life-threatening. These almost exclusively concern cyclosporin, anticoagulants, digoxin, antidepressants and protease inhibitors, with the herb St John's wort. Ginkgo and ginseng are also implicated in a number or reports, but many of these are unsubstantiated or may be idiosyncratic. The most common drugs that have been reported to interact with herbs are those involving the cardiovascular, central nervous and immune systems. Additional drugs treating other systems have also been implicated, however, examples are very limited. It is reasonable to assume that adding herbal products to a regimen of prescription drugs taken for the same purpose would lead to additive effects, and the answer to that lies in patient education. Although many herbal drugs are safe, it must be borne in mind that herbal supplements are intended to be taken over an extended period of time, which provides the opportunity for enzyme induction and other mechanisms of interaction to take effect. As far as advising patients is concerned, it is expedient not to be seen as scaremongering, otherwise patients may feel that the medical establishment is over-reacting and that drug companies are being self-serving, and if that happens even sound advice will be ignored. Articles exaggerating the problem, by treating hypothetical situations as fact, do not serve the users of herbs or the medical and pharmaceutical professions well, although they are often given undue prominence in the press.

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