INTERACTIONS OF HERBS WITH OTHER MEDICINES

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Introduction

The European market for phytopharmaceuticals in 1995 was reported to be US $ 1,098 million and it was estimated that this would increase to US $ 1,375 million by the year 2001.[1] The market for botanical health-care remedies in the USA was reportedly US $ 3.24 billion in 1996 with some 60 million people using herbs to treat minor ailments such as allergies, burns, colds, depression, headache, insomnia, premenstrual syndrome and rashes.[2] Surveys carried out in the USA[3] and Australia[4] indicate that substantial numbers of people are using complementary health treatments including herbs and herbal products. There are a number of reasons for the popularity of herbal remedies including their use as alternatives to potent pharmaceutical medicines, many of which have the ability to cause adverse reactions. Herbal products which are licensed as medicines in the UK are subject to strict labelling requirements and it is not permitted to make claims for the treatment of serious medical conditions unless clinical efficacy has been proven by clinical trials and approved by the Medicines Control Agency (MCA). Such products are allowed to make claims for the symptomatic relief of more minor conditions, providing it is demonstrated that suitable bibliographic evidence supports the claim. The majority of herbal products available to the general public in the UK are not licensed as medicines and are not subject to stringent medicines legislation. Although it is unlawful for medical claims to be printed on the label of such products, there is an abundance of literature on the alleged medical properties of the herbal ingredients present. The patient/consumer is thus able to self-select such herbal products sold over the counter in order to treat medical conditions. The use of herbal medicines in Europe, their legal requirements and issues affecting their quality, safety and efficacy have been reviewed previously.[5]

It is well established that patients taking more than one pharmaceutical medicine can experience drug interactions which may be detrimental to their health.[6] Pharmacodynamic interactions may occur between two drugs which have similar or antagonistic pharmacological effects or side effects. Some interactions are of a pharmacokinetic nature in which one drug may alter the absorption, distribution, metabolism or excretion of another drug. Drug-drug interactions may well be harmless for the vast majority of patients but for a minority of patients there may be harmful side effects. Drug interactions not only occur between drugs but may involve interactions with foods and beverages, e.g:-

alcohol enhances the anticoagulant effect of warfarin and the sedative effect of antidepressants; the ACE inhibitor verapamil used for the treatment of angina, arrhythmia and hypertension may increase blood alcohol levels.

grapefruit juice increases the plasma concentration of some dihydropyridine calcium channel blockers such as nifedipine used for the treatment of angina and hypertension.

cheese, beans, yeast extracts contain tyramine which may exert pressor effects on monamine oxidase inhibitor drugs (MAOIs) such as phenelzine used as an antidepressant, giving rise in blood pressure and producing throbbing headaches.

Combined herbal preparations may contain ingredients which interact with each other and an example may be taken from the Chinese Pharmacopoeia monograph for liquorice which states that it is used as a common ingredient in many traditional Chinese medicines prescriptions because it reduces the toxicity of other herbal ingredients.[7]

It is not unreasonable to propose that patients taking pharmaceutical drugs as part of their medical treatment, may also be taking herbs or herbal products. The question therefore arises as to whether herbal medicines interact with other medicines.

Potential for herb-drug interactions

There is only limited information available in the literature concerning the interaction of herbal medicines and conventional medicines.[8,9] The findings of a five year toxicological study on traditional remedies and food supplements used in the UK have been reported by the Medical and Toxicological Unit of Guy's and St Thomas' Hospital, London.[10] Their assessments were based on reports to the National Poisons Information Service, London, which provides emergency information to medical professionals, and from a follow-up questionnaire, clinical consultations, toxicological analyses and botanical identifications. Over 1200 enquiries were evaluated and an association was established in 785 cases of which only 12 were actually confirmed, the remainder being classified as probable/possible. These findings highlighted allergic reactions, liver problems and heavy metal poisoning from some Asian remedies. The largest single group of enquiries on herbal products involved sedatives, generally containing valerian and/or passiflora, producing drowsiness, gastro-intestinal distur-

bances and liver abnormalities.[10] Herbal laxative preparations reportedly caused abdominal pain and diarrhoea in some patients. There were relatively few cases involving interactions between herbal remedies and pharmaceutical medicines and none of them were proved conclusively. Four possible types of interaction were reported, papaya extract/warfarin (increased plasma levels of warfarin), devil's claw/warfarin, ginkgo/thiazide diuretics (hypertension) and evening primrose oil/anaesthetics (seizure).[10]

It might be concluded from these findings that there is no problem posed to patients by interactions between herbal remedies and conventional pharmaceutical drugs. Nevertheless, before dismissing this out-of-hand, the potential for such interactions should be evaluated. Consideration of the potential for herb-conventional pharmaceutical drug interactions have been reviewed previously[5] and a selected summary of some possible interactions is given in Table 1. Some herbs contain constituents which have the potential to interact with pharmaceutical drugs used to treat a wide range of disorders, e.g. the gastro-intestinal tract, cardiovascular, central nervous and endocrine systems. In general, the herb may either potentiate or antagonise effective drug treatment whilst in some instances, existing toxicities of conventional pharmaceutical drugs may be enhanced.

Gastro-intestinal system The efficacy of antacids or anti-ulcer drugs used in therapy may be affected in individuals taking herbs such as horse chestnut which is irritant to the gastro-intestinal tract. It is possible that the activity of a laxative may be potentiated or its side effects increased by concomitant use of a herbal laxative such as senna. (Table 1).

Cardiovascular system A number of pharmaceutical drugs with different modes of action may be prescribed for cardiovascular abnormalities. Are we sure that a cardiovascular-active herb such as hawthorn does not interact with cardenolide, anti-arrhythmic or b-blocker therapy? Diuretics are commonly prescribed for the management of hypertension and their activity may be potentiated by co-administration of herbal diuretics such as dandelion. Elderly patients, in particular, are susceptible to the side effects of diuretics. Herbs which either lower blood pressure (e.g. ginseng) or raise it (e.g. broom), or have mineralocorticoid activity (e.g. liquorice) or are diuretic (e.g. dandelion) may adversely affect the beneficial clinical effects of antihypertensive therapy. Blood lipid levels, already lowered by treatment with lipid-lowering drugs, may be further reduced by the use of hypolipidaemic herbs such as alfalfa. Any herb with cardioactive, hypertensive or hypotensive action may interfere with nitrate drugs (e.g. isosorbide dinitrate) which are potent coronary dilators or with calcium channel blocking drugs (e.g. nifedipidine) used to treat angina, hypertension and arrhythmias. A number of herbs contain sympathomimetic amines, e.g. parsley, and there is the risk of developing hypertension when used with pharmaceutical medicines which also have sympathomimetic action (e.g. isoprenaline, ephedrine). Anticoagulant therapy is important for the control of thrombosis and warfarin is one of the most frequently prescribed drugs. There are a large number of drug-drug interactions recorded for warfarin[6] and a number of herbs have the potential to potentiate or to antagonise warfarin. Herbs, such as angelica, which contain coumarins have anticoagulant activity whereas other herbs, such as agrimony, are reported to have coagulant activity. Aspirin increases the risk of bleeding in warfarin therapy and it is possible that herbs such as willow, which contains salicylates may have similar effects. Therapeutic doses of garlic should not be given to patients with slow blood clotting time and caution is recommended for those on anticoagulant therapy.[5]

Central nervous system Hypnotics and anxiolytics may react with sedative herbs, e.g. passiflora, valerian, or with stimulant herbs, e.g. ginseng. Evening primrose oil may have the potential to manifest undiagnosed temporal lobe epilepsy and caution should be exercised in patients taking epileptogenic drugs such as phenothiazines. Herbal sedatives, e.g. hypericum, may affect the activity of antidepressant drugs and it is possible that any sedative herb may interfere with the activity of analgesic and antiepileptic drugs. (Table 1).

Endocrine system Drugs acting on the endocrine system including antidiabetics, corticosteroids and oral contraceptives may interact with herbal remedies. Alfalfa has hypoglycaemic activity whereas devil's claw is reportedly hyperglycaemic and therefore it is possible that co-administration of these herbs with conventional diabetic therapy may result in adverse effects. Ginseng and red clover have sex hormonal activity and may have the potential to interfere in the effectiveness of sex hormone treatment, including oral contraceptives. (Table 1).

Conclusions

Drug-drug interactions may have little or no effect in patients and some are harmless. For those drug-drug interactions which are potentially harmful, the effects may only occur in a small proportion of patients.[6] However, serious interactions can occur and these may be life threatening or require hospitalisation. Some drugs have a small therapeutic ratio (toxic dose/therapeutic dose) e.g. phenytoin, and a series of other drugs require careful control to be maintained of their dosages, e.g. anticoagulants, antihypertensives, antidiabetics. These drugs are the ones which are most frequently involved in interactions. Patients with impaired renal or liver functions, or elderly, are at most risk from drug interactions and may be more prone to adverse effects.

Health-care professionals providing pharmaceutical medicines for the treatment of disease should be aware that concomitant use of herbal remedies may be the reason for an unexplained toxic effect or lack of medical efficacy. Likewise, consumers

purchasing herbal remedies or herbalists treating patients should be aware of potential herb-drug interactions. Education and continuing education programmes for health-care professionals should include information on drug-drug, drug-food and drug-herb interactions. There is a continued need for surveillance and it is essential that interactions, which may occur in only a minority of the population, are recognised. Suspected drug-herb interactions should be reported to medicines' regulatory authorities. In the UK, the MCA yellow warning card system is now extended to include not only licensed herbal medicinal products but also non-licensed products. As with all drug interactions continued pharmacovigilance is necessary to detect potential drug-herb interactions, especially when the incidence of such reactions is low. The clinical outcome may well be significant albeit in a small number of patients.

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Table 1 **Potential for conventional pharmaceutical medicine - herb interaction**

Therapeutic category/ type of medicine	Herb action	Herb example
Gastrointestinal system		
antacid, anti-ulcer	irritant to gastrointestinal tract	horse chestnut
antidiarrhoeal, laxative	laxative	senna
Cardiovascular system		
cardiac glycoside, anti-arrhythmic, β-blocker	cardioactive	hawthorn
	hypertensive	ginseng
	hypertensive	broom
	mineralocorticoid	liquorice
	amine constituent	calamus
	diuretic	dandelion
diuretic	diuretic	dandelion
lipid lowering	hypolipidaemic	alfalfa
nitrates, calcium channel blockers	cardioactive, hypo- and hypertensive	
sympathomimetic	amine constituents	parsley
	hypo- and hypertensive	
anticoagulant	anticoagulant	angelica
	coagulant	agrimony
	salicylate	willow
Central nervous system		
anxiolytics, hypnotics	sedative	passiflora, valerian
stimulant	stimulant	ginseng
antipsychotic	diuretic	dandelion
	manifests undiagnosed epilepsy	evening primrose
antidepressant	amine constituents	parsley
	sedative	hypericum
analgesic	diuretic	dandelion
	sedative	hypericum
antiepileptic	sedative	hypericum
	manifests undiagnosed epilepsy	evening primrose
Endocrine system		
antidiabetic	hypoglycaemic	alfalfa
	hyperglycaemic	devil's claw
corticosteroid	diuretic	dandelion
	mineralocorticoid	liquorice