

## Herbal remedies: promises with risk

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The adage, “what goes around comes around”, seems applicable to the current popularity of herbal remedies. Plants have been used throughout human history for their medicinal properties. Five hundred years ago botanical gardens were maintained as a source of medicinal plants [1], but this gave way to “modern medicine” at the beginning of the 20<sup>th</sup> century, when scientific method predominated and herbal remedies were relegated to the level of quackery. Today patients have become enlightened consumers and are again embracing herbal (phytomedicinal) remedies [2], but caution is in order.

This consumer-driven trend originated in part by a desire of patients to be more self-reliant, the naïve view that what is natural can only be good, the perceived or real failure of conventional pharmaceuticals to deliver expected results (especially in chronic conditions), the notion that herbal remedies, in contrast to conventional drugs, are completely innocuous, and the recognition of the value of traditional medicines [3, 4]. Small and even major pharmaceutical companies are aggressively expanding the market for these products. Many countries impose regulatory control over the sale of specific herbal remedies. In 2003, in the USA, the FDA proposed a new rule for Good Manufacturing Practise in the manufacturing, packing, and holding of herbal drugs currently sold as dietary supplements, not only in drug stores, but also in health food stores and supermarkets. In 2004 the European Commission (which governs the EU) introduced a simplified procedure for traditional herbal preparations that will allow a premarket assessment of safety and quality. The worldwide economic impact of herbal remedies is immense. In the U.S. alone, in 1997 it was estimated that 12.1% of the population spent \$ 5.1

billion on herbal remedies [5]. In the UK, sales of herbal remedies were worth £ 75 million in 2002, an increase of 57% over the previous 5 years [6]. Studies carried out in other countries, such as Australia and Italy, also suggest an increasing prevalence of use of herbal medicinals among the adult population [7, 8]. The growing trend in the use of herbal remedies includes self-medication for such diverse conditions as insomnia, anxiety, fatigue, attention deficit disorder, hypercholesterolemia, prostate enlargement, menstrual and menopausal symptoms, musculoskeletal disorders and even Acquired Immunodeficiency Syndrome [9]. Importantly, 70% of patients who use herbal products do not reveal this to their physician or pharmacist [8], greatly increasing the risk of adverse reactions from the interactions between herbal components and concurrent pharmacotherapy. Improved reporting is now making it clear that there are potentially serious interactions between some common herbal remedies and widely used synthetic pharmaceuticals [10]. In particular, it is important to recognize the dangers of combining ginkgo with anticoagulants and anti-platelet drugs, which may lead to intracerebral hemorrhage or spontaneous bleeding, respectively. This effect is most likely due to the inhibitory effect of gingolides on platelet-activating factor [11]. Other common natural products with the potential to interfere with anti-clotting drugs are garlic and horsechestnut [12]. Another troubling adverse effect, long recognized for certain herbal products (particularly those containing pyrrolizidine alkaloids), is hepatotoxicity [13-15].

Indeed, plants have served man well through the ages. Although they are not without untoward effects, consider the impact made by atropine (*Atropa belladonna*), digoxin (*Digitalis purpurea*), colchicine

(*Colchicum autumnale*), codeine (*Papaver somniferum*), vincristine (*Catharanthus roseus*), ipecac (*Cephaelis ipecacuana*), taxol (*Taxus brevifolia*), physostigmine (*Physostigma venenosum*), senna (*Cassia acutifolia*), ephedrine (*Ephedra sinica*), capsaicin (*Capsicum frutescens*), scopolamine (*Datura fastuosa*) and artemisinin (*Artemisia annua*). Over the years these drugs, used under medicinal supervision, have relieved human suffering due to their intrinsic properties and by serving as models for the development of even more specific synthetic pharmaceuticals.

Even though adverse effects should be anticipated from natural medicines, virtually none of the multitude of herbal products widely available today has been properly evaluated in clinical studies for untoward effects. Certainly there is substantial evidence for adverse reaction to some medicinal plants (Table 1). The situation is complicated in several ways: the sources of herbal material are diverse; the active (and toxic) components vary as a result of climate, soil quality, genetic factors and exposure to chemicals; quality control is lacking so that problems such as contamination with heavy metals and microorganisms, and adulteration with chemicals may arise during preparation, storage or

shipping of the final product [16]. Common adulterants include aminopyrine, aspirin, betamethasone, caffeine, chlordiazepoxide, chlorpheniramine, diazepam, diclofenac, ephedrine, indomethacin, paracetamol, thiazide diuretics and theophylline. Specific examples of adulteration and the safety of herbal medicines were recently discussed in a series of reports [5, 17]. Standardization would seem to be a step forward, but this makes little sense when most medicinal herbs have yet to yield the identity of their pharmacologically-active constituent(s). Attempts at standardization are confounded by the complex composition of herbs; active constituents - antagonists as well as agonists - may co-exist [8, 18, 19]. The desired effect may require concerted action of some or all of the particular herb's components. For this reason too, differences in desired/undesired activities, and potency differences may be noted when comparing whole herb, infusion and extract. The problem is to determine the active component upon which standardization will be based. It has been recently recognized that *Echinacea angustifolia* and St. John's wort appear to be improperly standardized for therapeutic activity by their levels of echinacosides and hypericin/ hyperforin, respectively [19, 20].

**Table 1:** Examples of adverse effects that may occur with herbal remedies<sup>a</sup>.

Herbal drug (Plant)	Adverse effects	Indication	Constituent responsible	Potential interaction
Echinacea ( <i>Echinacea</i> spp)	Gastrointestinal disturbances	Acute upper respiratory infection	Polysaccharides	Immunosuppressants <sup>b</sup>
Feverfew ( <i>Tanacetum parthenium</i> L.)	Gastrointestinal disturbances, hypersensitivity reactions	Migraine prophylaxis	Sesquiterpene lactones	Anticoagulants
Garlic ( <i>Allium sativum</i> L.)	Gastrointestinal complaints, allergic reactions	Raised blood cholesterol	Sulphur containing compounds	Anticoagulants/ antiplatelets
Hawthorn ( <i>Crataegus monogyna</i> L.)	Nausea, dizziness, fatigue	Heart failure	Procyanidins	Cardiac glycosides
Kava ( <i>Piper methysticum</i> G. Forst.)	Liver damage	Anxiety	Kavapyrones	Anti Parkinson, sedatives
Milk thistle { <i>Silybum marianum</i> (L.) Gaertn.}	Gastrointestinal problems	Liver diseases	Flavonolignans	Metabolized by hepatic enzymes
Saw palmetto { <i>Serenoa repens</i> (W. Bartram) Small}	Gastrointestinal complaints, dysuria, decreased libido	Benign prostrate hyperplasia	Phytosterols	Hormonal therapy
St. John's wort ( <i>Hypericum perforatum</i> L.)	Allergic reactions, gastrointestinal symptoms, dizziness/vertigo, tiredness/fatigue	Mild/moderate depression	Hyperforin	Metabolized by hepatic enzymes or eliminated through induction of P-glycoprotein

<sup>a</sup>Data extracted from Capasso *et al.*, 2003

<sup>b</sup>No clinical cases of drug interactions have been reported.

Clearly more research into all aspects of herbal therapy is warranted. The resurgence of interest in herbal remedies presents a challenge of identifying and characterizing the constituents of herbal remedies, standardizing the products in a manner appropriate to the intended use, and to discourage the indiscriminate use and misuse. Until better control of

herbal remedies is gained on several levels it seems prudent to follow the suggestion of Barnes and apply “phytopharmacovigilance” [6], that is, systematic research of the safety of herbal medicines into the marketing and use of herbal remedies.

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