How Safe are Herbal Products?

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In the search for cures for his ailments, man discovered many healing and toxic properties of plants. Some were found to cure certain diseases while others were found to exert dramatic effects on the body[1]. Consequently, most natural products used today as medicines are derived from plants.

In recent decades, the growing awareness of the possible toxicity of modern medicinal products has contributed to a rise in interest, on the part of the general public, in alternative medicinal therapies. This phenomenon is also evident in Malta, as demonstrated by the increasing availability of herbal remedies from pharmacies. Unfortunately, there exists a remarkably common belief among suppliers and users of herbal remedies that the products are harmless because they are derived from a natural source. However there is a substantial body of evidence to rebut this view[2].

The pharmacological activity and toxicity of conventional medicines can be attributed to a drug substance or combination of substances, or to the metabolic products that are generated in the body. Herbal medicines exert their activity and effects in very much the same way but little is known about the kinetic behaviour of the bioactive compounds in the plants. However complex the composition of a herbal medicine may be, the active principles are chemical entities that possess pharmacodynamic properties and must obey the same pharmacokinetic rules as conventional medicines[2].

Toxicity of Herbal Ingredients

Plants have evolved defence mechanisms against predation by animals and pests. These include chemicals that make the plants unpalatable or that poison or kill the predators, and may therefore be the cause of toxicity in humans. Thus the coexistence of beneficial and adverse effects is as much a reality for plant products as it is for conventional medicines[3].

The toxic effects of phytochemical substances are varied when consumed by mammals. The main target organs appear to be the liver and the kidneys, probably because of their role in the metabolism and elimination of xenobiotics. Plant substances may also possess carcinogenic, teratogenic, mutagenic, or genotoxic properties that increase their toxic effects.

The safety of herbal remedies is of particular importance since the majority of these products are self-prescribed and are used to treat minor and often chronic conditions. The long-term traditional use of a plant, even for many hundreds of years, does not necessarily establish its safety. The more subtle and chronic forms of toxicity, such as carcinogenicity, mutagenicity and hepatotoxicity, may well have been overlooked by previous generations but are of concern nowadays when assessing product safety[9].

Herbal products are often the target of criticism because of their unique status when compared with other medicines. Conventional medicinal products must undergo extensive preclinical testing in laboratory animals for the evaluation of organ toxicity and death, tests for mutagenic and carcinogenic activity, and reproductive toxicity before they are administered to human beings in clinical trials. However, it is ironic to note that much of the knowledge on the toxicity of herbal products that has been accumulated over the years stems from observed poisonous and lethal effects in man[3].

The difficulty with which the herbal active principles may sometimes be isolated or identified means that the source of toxicity may at times be unknown. Furthermore, errors in the identification of the species of plant or plant parts and difficulty in the standardisation of the content of active principles may lead to toxicity especially in self-medication.

Adverse Reactions

The inherent toxic properties of herbal ingredients may be the cause of adverse effects arising from the ingestion or topical application of herbal products. This is even more so when the products do not contain adulterants or substituted ingredients that however may in themselves be the cause of adverse reactions[8]. Some herbal ingredients that may potentially give rise to adverse events as reported in the literature are summarised in Table I.

Herbal products have traditionally been used to treat both adults and children. Although herbal remedies may offer a milder alternative to some conventional medicines, they must be used with caution in children and medical advice should be sought if in doubt. Babies may be at a higher risk of toxic effects because they may be given higher doses than adults per kilogram of body weight, they lack certain drug metabolising and detoxifying enzymes, and they may receive herbal ingredients from the mother during lactation[10]. Chamomile, a popular remedy for teething pains in babies, is known to contain allergenic sesquiterpene lactones and should be used with caution. The administration of herbal teas to children is generally unwise unless used according to

professional advice[9].

The chemistry and pharmacology of a number of herbs are poorly documented and their use in pregnancy should be avoided. In addition to the herbs indicated in Table I, other herbs that should be used with caution in pregnancy include Avens, Burdock, Calendula, Devil's Claw, Euphorbia, Fenugreek, Gentian, Hawthorn, Black Horehound, Meadowsweet, Myrrh, Passionflower, Poplar, Northern Prickly Ash, Raspberry, Uva-Ursi, Vervian, and Willow. Some of the herbs are reputed to be abortifacient or to affect the menstrual cycle although no recent clinical or experimental data exists. Others are oxytocic, demonstrate uterine activity or are uterine stimulants, demonstrate hormonal activity, or are inherently toxic[9].

As is the case with conventional medicines, the serious and lethal adverse effects of some herbal ingredients may arise as a result of misuse or abuse of preparations or due to a lack of knowledge regarding the substances. The abuse of herbal products as alternatives to street drugs is an area of concern. This is evidenced by the use of *Ephedra* as an alternative to 4-methyl-2-dimethoxyamphetamine (MDMA, 'Ecstasy') because of its euphoric effect[6]. In fact, the United Kingdom (UK), United States of America (USA) and Canada have issued warnings against the use or supply of *Ephedra*-containing herbal food supplements[4,5]. The Food and Drug Administration of the USA has also ordered the removal from the market of preparations containing *Ephedra*, alone or in combination with St John's Wort, that were promoted as herbal alternatives to fenfluramine and

Table I: Potential Adverse Effects of Herbal Ingredients (adapted from Newall *et al.*, 1996)

Herb	Adverse Effect
Agnus Castus[2]	Allergic reactions
Alfalfa	Systemic lupus erythematosus syndrome
Aloes[2]	Purgative, irritant to GIT
Angelica	Phototoxic dermatitis
Aniseed	Contact dermatitis
Apricot[1,2]	Cyanide poisoning (seed)
Arnica[1]	Dermatitis, irritant to GIT
Artichoke	Allergenic, dermatitis
Asafoetida[2]	Dermatitis, irritant
Bayberry	Carcinogenic to rats
Blue Flag[2]	Nausea, vomiting, irritant to GIT and eyes (fresh root)
Bogbean[2]	Purgative, vomiting (in large doses)
Boldo[2]	Toxicity, irritant
Boneset[2]	Dermatitis, cytotoxic
Borage[1,2]	Genotoxic, carcinogenic, hepatotoxic
Broom[2]	Cardiac depressant
Buchu[2]	Irritant to GIT, kidney
Calamus[1]	Carcinogenic, nephrotoxic, convulsions
Capsicum	Irritant
Cascara[2]	Purgative, irritant to GIT
Cassia	Allergenic, irritant
Celery	Phototoxic, dermatitis
Cereus	Irritant to GIT (fresh juice)
Chamomile[2]	Allergic reactions
Chaparral[2]	Dermatitis, hepatotoxic
Cinnamon	Allergenic, irritant
Clove	Irritant
Cohosh, Black[2]	Nausea, vomiting (high doses)
Cohosh, Blue[2]	Irritant to GIT (seeds)
Cola[2]	Sleeplessness, anxiety, tremor
Coltsfoot[1,2]	Genotoxic, carcinogenic, hepatotoxic
Comfrey[1,2]	Genotoxic, carcinogenic, hepatotoxic
Corn Silk[2]	Allergenic, dermatitis
Cowslip	Allergenic
Damiana[2]	Convulsions (one report with high dose)
Dandelion	Allergenic, dermatitis
Echinacea	Allergenic, irritant
Elecampane	Allergenic, irritant
Eucalyptus[2]	Nausea, vomiting
Evening Primrose Oil	Mild indigestion, increased risk of epilepsy (in schizophrenics on phenothiazines)
Eyebright	Mental confusion, raised intraocular pressure (tincture)
Feverfew[2]	Allergenic, dermatitis
Frangula[2]	Purgative, irritant to GIT
Fucus[2]	Hyperthyroidism
Garlic	Irritant to GIT, dermatitis

Herb	Adverse Effect
Ginkgo	Gastric upset, headache
Ginseng[2]	Mastalgia, vaginal bleeding, insomnia
Golden Seal[2]	Gastric upset
Gravel Root[1]	Genotoxic, carcinogenic, hepatotoxic
Ground Ivy[2]	Irritant to GIT, kidneys
Guaiacum	Allergenic, dermatitis
Hops[2]	Allergenic, dermatitis
Horehound, White[2]	Dermatitis, irritant (plant juice)
Horse-chestnut	Nephrotoxic
Horseradish[2]	Allergenic, irritant
Hydrangea	Dermatitis, irritant to GIT
Hydrocotyle[2]	Phototoxic, dermatitis
Ispaghula	Oesophageal obstruction, flatulence (if swallowed dry)
Jamaica Dogwood[2]	Irritant, numbness, tremors (high doses)
Juniper[2]	Irritant, abortifacient
Lady's Slipper	Allergenic, dermatitis, hallucinations
Liferoot[1,2]	Genotoxic, carcinogenic, hepatotoxic
Liquorice[2]	Hyperaldosteronism (excessive ingestion)
Lobelia[2]	Nausea, vomiting, diarrhoea
Maté[2]	Sleeplessness, anxiety, tremor
Mistletoe[2]	Hepatitis, hypotension, poisonous
Motherwort[2]	Phototoxic dermatitis
Nettle[2]	Irritant
Parsley	Irritant, hepatitis, phototoxic, abortifacient (excessive ingestion)
Pennyroyal[2]	Irritant, nephrotoxic, hepatotoxic
Pilewort[1]	Irritant
Plantain[2]	Allergenic, dermatitis, irritant
Pleurisy Root[2]	Dermatitis, irritant, cardiac activity
Pokeroot[2]	Mitogenic, toxic, nausea, vomiting, cramp
Prickly Ash, Southern[2]	Toxic to animals
Pulsatilla[1,2]	Allergenic, irritant
Queen's Delight[1,2]	Irritant to GIT
Red Clover[2]	Oestrogenic
Rhubarb[2]	Purgative, irritant to GIT
Rosemary	Convulsions
Sage	Toxic, convulsant
Sassafras[1,2]	Carcinogenic, genotoxic
Scullcap[2]	Hepatotoxicity
Senega	Irritant to GIT
Senna[2]	Purgative, irritant to GIT
Shepherd's Purse[2]	Irritant
Skunk Cabbage[2]	Itch, inflammation
Squill[2]	Irritant, cardioactive
St John's Wort[2]	Phototoxic
Tansy[1,2]	Severe gastritis, convulsions
Thyme	Irritant to GIT
Wild Carrot[2]	Phototoxic, dermatitis
Yarrow[2]	Allergenic, dermatitis
Yellow Dock[2]	Purgative, irritant to GIT

GIT - Gastrointestinal tract [1] Not recommended for internal use [2] Herbal ingredients best avoided or used with caution during pregnancy.

fentermine[7]. Furthermore, warnings against abuse of products containing Khat and Yohimbe as alternatives to street drugs were issued in the UK[4].

Drug-Herb Interactions

A recent circular from the Maltese Health Division highlighted the interactions between herbal remedies containing *Hypericum perforatum* (St John's Wort) and conventional medicines[11]. However, very few drug-herb interactions have been reported in the medical literature when compared with reports of interactions between conventional drugs. The low incidence of reporting of interactions with herbs, in itself, neither confirms their safety in use nor suggests that the incidence is indeed low. Most of the interactions are not recognised by patients who self-medicate and are not reported to a medical practitioner or a pharmacist[12].

The mechanism of a drug-herb interaction may be difficult to identify when there is insufficient knowledge of the pharmacological activity of the herbal product. However, it is possible to predict potential interactions on the basis of known herbal constituents and their reported pharmacological action and documented side effects[9]. Examples of known or potential drug-herb interactions are summarised in Table II. It should be emphasised that many drug interactions are harmless and many of those that are potentially harmful occur only in a small proportion of patients and may then vary in severity from patient to patient[6].

Table 2: Summary of Drug-Herb Interactions of Commonly Used Drugs (adapted from Miller, 1998)

Drug	Herb	Interaction
Alprazolam	Kava	Excessive sedation may result with concomitant use.
Corticosteroids, Cyclosporin	Echinacea, Astragalus, Liquorice, Alfalfa Sprouts	Immunostimulating effects of the herbs may offset immunosuppressive effects of the drugs.
Digoxin		Additive effects possible with herbs containing cardiac glycosides.
	Hawthorn	Hawthorn purportedly potentiates digoxin.
	Liquorice	Liquorice may cause hypokalaemia, hence predisposing the patient to toxic effects of digoxin.
	Foxglove	Plantain may be adulterated with Foxglove, hence elevating blood levels of digoxin.
	Siberian Ginseng, Kyushin	The herbs may interfere with digoxin assays.
	Uzara root	Uzara root may exert additive digoxin-type cardiac effects.
Diuretics (e.g. hydrochloro-thiazide, furosemide)	Sodium-sparing herbal aquaretics (e.g. Dandelion, Uva-Ursi)	The herbs may offset antihypertensive effects of the drugs.
	Gossypol	Gossypol may exacerbate hypokalaemia secondary to the drugs.
Hypoglycaemics (e.g. sulphonylureas)	Karela	Karela has been shown to decrease dosage requirements for chlorpropamide.
Iron	Tannin-containing herbs (e.g. Chamomile, Feverfew, St John's Wort)	The herbs may interact with iron, hence inhibiting iron absorption.
Levothyroxine	Horseradish, Kelp	The herbs may suppress thyroid function, complicating thyroid function.
Nonsteroidal anti-inflammatory drugs	Herbs irritant to GIT (e.g. Gossypol, Uva-Ursi)	Additive GIT irritation may be encountered with concomitant use.
Phenelzine (and other MAO inhibitors)	Ginseng, Yohimbine, Ephedra	Concomitant use with the herbs may result in insomnia, headache and tremulousness.
	St John's Wort, Liquorice	The herbs may have MAO inhibitor activity and should not be used concomitantly with known MAO inhibitors.
Phenobarbitone	Thujone-containing herbs (e.g. Wormwood, Sage)	The herbs may lower seizure threshold, hence increasing anticonvulsant dosage requirements.
	Gamolenic acid-containing herbs (e.g. Evening Primrose Oil, Borage)	The herbs lower seizure thresholds and may increase anticonvulsant dosage requirements.
Phenytoin		Same as for phenobarbitone.
	Shankhapulshpi	Shankhapulshpi may shorten the half-life and diminish effectiveness of phenytoin.
Spironolactone	Liquorice	Liquorice may offset the effects of spironolactone.
Warfarin	Garlic, Ginger, Ginkgo, Feverfew	The herbs may augment the anticoagulant effect of warfarin.
	Ginseng	Ginseng may decrease the effectiveness of warfarin.

GIT - Gastrointestinal tract MAO - Monoamine oxidase

Conclusion

The ultimate benefit that the consumer will derive from the use of herbals depends on the correct use of products of acceptable quality. This may be achieved if there is adequate control of the manufacture of herbal products to ensure that the correct standardised botanical ingredients are used and to minimise the problem of toxicity associated with adulteration, substitution, misidentification and contamination of products[13].

Different standards of regulatory control of herbal products exist in various countries. When preparations are sold without appropriate or complete labelling and product information, or when they are freely available as unlicensed dietary supplements, it becomes increasingly difficult to enforce quality and safety requirements or to ensure that all incriminated products are withdrawn after a drug alert[8].

The examples of herbal toxicity that were presented in this brief discussion are not intended to undermine the role of herbal medicines in pharmacotherapy but, rather, to demonstrate that natural products are composed of chemical substances that possess properties that can be therapeutic as well as toxic. Herbal medicines should be allowed to find a niche in pharmacotherapy, not solely as an alternative form of therapy but also to complement conventional drugs. ✶

References

1. Samuelsson G. Drugs of Natural Origin. Stockholm: Swedish Pharmaceutical Press; 1992.
2. De Smet P.A.G.M. Drugs used in non-orthodox medicine. In: Dukes M.N.G., editor. Meyler's Side-Effects of Drugs. Amsterdam: Elsevier Science Publishers; 1992.
3. Sheehan D.M. Herbal medicines, phytoestrogens and toxicity: Risk:benefit considerations. Proceedings of the Society for Experimental Biology and Medicine 1998: 217:379-385.
4. WHO. Warning of herbal products sold as alternatives to abuse drugs. WHO Drug Information 1997: 11:252.
5. WHO. Ephedrine in food supplements. WHO Pharmaceuticals Newsletter 1997: 9/10:3-4.
6. U.S. Department of Health and Human Services. FDA statement on street drugs containing botanical ephedrine. HHS News 1996: April 10:1.
7. WHO. Herbal "Fen-Phen": Warning concerning "natural" anti-obesity alternatives. WHO Pharmaceuticals Newsletter 1997: 11/12:2-3.
8. Forte J.S., Raman A. Regulatory issues relating to herbal products - Part 2: Safety and toxicity. Journal of Medicinal Food 2000: 3(1):41-57.
9. Newall C.A., Anderson L.A., Phillipson J.D. Herbal Medicines: A Guide for Health-care Professionals. London: The Pharmaceutical Press; 1996.
10. Huxtable R.J. The harmful potential of herbal and other plant products. Drug Safety 1990: 5(supplement 1):126-136.
11. Health Division, Malta. Important interactions between St John's Wort (Hypericum perforatum) preparations and prescribed medicines. DH Circular 2000: 69/2000(March 13).
12. D'Arcy, P.F. Adverse reactions and interactions with herbal medicines: Part 2. Drug interactions. Adverse Drug Reactions and Toxicological Reviews 1993: 12:147-162.
13. Forte J.S., Raman, A. Regulatory issues relating to herbal products - Part 3: Quality and its determination. Journal of Medicinal Food 2000: 3(1):59-69.
14. Miller L.G. Herbal medicines: Selected clinical considerations focusing on known or potential drug-herb interactions. Archives of Internal Medicine 1998: 158:2200-2211.