

HERBAL MEDICINAL PRODUCTS

Herbs have been used in medicine since the beginning of time. There are many references to the medicinal use of herbs with *Materia Medica*, written in the 1st Century, still one of the world's greatest reference sources on herbal medicinal products. Many of the drugs commercially available today are derived from plants e.g. digoxin from *Digitalis*, paclitaxel from *Taxus* (yew) species.

Self-medication with herbal medicinal products is widespread. Patients are often reluctant to inform allopathic practitioners that they are taking herbal medicinal products for fear of censure. Consequently, clinicians may not be alerted to the potential for drug-herb interactions and the side effects associated with them.^{1,2} In 1997, a USA study estimated that 70% of patients using herbal medicinal products did not inform their pharmacist or doctor of this.³ Doctors and pharmacists should routinely ask their patients about the use of herbal medicinal products. It is important that this is done in a non-judgemental manner to encourage the patient to report any adverse effects that he/she may have experienced.

Why Do People Use Herbal Medicinal Products?

The World Health Organisation estimates that 75% of the global population depends on botanical medicines for basic healthcare needs, particularly in developing countries.⁴ The herbal medicinal products market is a lucrative one even in the developed world; The Royal Pharmaceutical Society of Great Britain recently estimated that retail sales in the UK of aromatherapy essential oils and herbal and homeopathic preparations will total Stg£126m by 2002.⁵ In Ireland, the use of herbal medicinal products as alternatives or as adjuncts to conventional therapies has increased in recent years despite the increasing number of orthodox medicines. There are several reasons why people choose to use herbal medicinal products including:

- There is a perception that “natural equals safe”. This is not necessarily true as many commonly used medicines have been derived from natural sources and possess potent adverse effects in addition to therapeutic benefits.
- There is a perception that “more” adverse reactions occur with conventional therapies.
- Self-medication with herbal medicinal products may provide a sense of control or psychological comfort for the patient. This is particularly evident in those patients for whom conventional medicines cannot provide any further benefits e.g. chronic conditions such as eczema, arthritis.
- Patients may have cultural, religious or ecological reasons for using herbal medicinal products.

It has been suggested that the use of herbal medicinal products is greater in Caucasians, those with higher income, education and aged 25-50 years.³

There are a number of problems associated with herbal medicinal products as shown in Table 1.

Table 1: Problems Associated With Herbal Medicinal Products⁶

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| <ul style="list-style-type: none">• Need for improved quality control and standardisation. - Herb potency may vary due to climate and soil conditions therefore the potency and purity can vary between different batches of the same herbal product.• Adulteration - Other herbs, heavy metals or pharmaceutical drugs for example, may have been added in an attempt to enhance the efficacy of some herbal preparations.• Little control on the labelling of these preparations - Inappropriate indications and claims can be made.• Like conventional therapies adverse reactions may occur.• Limited evidence of efficacy in the form of well-designed clinical trials.• The prescriber or pharmacist may be unaware that a patient is self-medicating with a herbal medicinal product thus increasing the likelihood of drug-herb interactions. |
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Four herbal medicinal products are discussed in more detail below. These agents have been chosen because of the number of requests for information received by the NMIC.

St. John's wort (SJW)

SJW is an aromatic perennial herb that is native to Europe but can now be found growing almost everywhere in the world.⁷ The genus *Hypericum* contains more than 300 species including *Hypericum perforatum*. Most preparations are standardised according to their hypericin content. However, there are many constituents in the flowering plant with biological activity including other naphthoquinone derivatives, flavonoids and hyperforin. Therefore standardisation of hypericum extracts on hypericin content alone may offer no guarantee of pharmacological bioequivalence.^{3,8} The use of SJW as a herbal healing agent dates back 2000 years and purported uses include sedation, diuresis, antiviral activity and wound healing. Most published information with regard to the therapeutic efficacy of SJW has been in relation to depression. The mechanism by which SJW exerts its anti-depressant action is unknown. A number of mechanisms have been postulated including inhibition of dopamine, noradrenaline and serotonin release and reduction in the expression of cytokine interleukin 6.^{3,7} In January 2000, SJW was classified as a prescription-only medicine although a preparation with a product authorisation is not available in Ireland.

A number of trials have examined the efficacy of SJW for the treatment of depression. Most have been flawed due to the methodology, selection criteria or rating scales used. A meta analysis of 23 randomised controlled trials, including a total of 1757 patients, found evidence that extracts of hypericum were more effective than placebo for the treatment of mild to moderate depression.⁹ A study by Woelk *et al* examined the use of hypericin 0.2% extract vs imipramine 75mg BD in a randomised study involving 324 patients. The treatments were found to be therapeutically equivalent with a lower incidence of adverse drug reactions being reported with the hypericum extract.¹⁰ A study by Philipp *et al* again compared hypericum extract (0.2-0.3% hypericin content) with imipramine 100mg daily and placebo. The hypericum extract

was found to be more efficacious than placebo and at least therapeutically equivalent to imipramine.¹¹

SJW has generally been found to be well tolerated. Adverse effects involving the gastrointestinal tract (constipation, dry mouth), skin (photosensitivity) and central nervous system (fatigue) being most commonly reported.^{3,7,8,12} No information is available on the use of SJW in special populations such as pregnant and lactating mothers and its use is best avoided in these groups.^{3,8} The safety of concurrent administration of SJW with prescription or OTC medication has not been established. SJW is known to be an inducer of cytochrome P450 and this has led to a number of documented interactions with prescription drugs. (Table 2)

Table 2: St John's wort - Drug Interactions

DRUG	POSSIBLE OUTCOME
SSRIs/Triptans ^{7,13}	↑ risk of serotonin syndrome
Theophylline ²	↓ serum theophylline levels
Digoxin ²	↓ AUC & ↓ peak & trough digoxin concentrations
Warfarin ¹⁴	↓ INR
Cyclosporin ¹⁵	↓ serum cyclosporin levels
Indinavir & other protease inhibitors/Non-nucleoside reverse transcriptase inhibitors ¹⁶	↓ serum concentrations of antiretrovirals
Oral contraceptive pill ¹⁷	↓ oestrogen levels - ? contraceptive failure

Ginkgo Biloba

Ginkgo is obtained from the leaves of the ornamental tree *Ginkgo biloba*. Throughout history Ginkgo has been used as an anti-microbial, an anti-inflammatory, a vasodilator and for the treatment of diminishing mental and physical health with increasing age.^{3,18} Like SJW, Ginkgo biloba is a prescription-only medicine in Ireland with two products authorised in Ireland.¹⁹ Ginkgo contains three groups of compounds which are thought to contribute to its overall effect namely flavonoids, diterpenes and sesquiterpenes.^{8,18,20} The demonstrated effects of Ginkgo include the following:

- Increased tolerance to ischaemic conditions
- Inhibition of platelet activating factor (PAF)
- Beneficial effect on neurotransmitter disturbance and cerebral receptor populations
- Prevention of membrane damage by acting as a free radical scavenger
- Anti-infective^{3,20}

Over 70 trials have been conducted using standardised Ginkgo biloba extract.²¹ A number of these trials evaluated the efficacy of Ginkgo biloba for dementia syndromes and peripheral vascular disease using extracts standardised for flavonoid

content.^{18,21} Eight trials investigating efficacy in the treatment of cerebral insufficiency were found to be of acceptable methodological quality and 7 of the 8 reported positive therapeutic outcomes.^{3,22} Treatment of intermittent claudication also met with reasonable success including relief of symptoms and improved walking distances.^{3,23} Preliminary clinical trials using Ginkgo biloba extract for Alzheimer's disease and dementia appear to be promising and Ginkgo may delay mental deterioration in the early stages of Alzheimer's disease. Doses ranged from 120-240mg standardised extract daily and 4-6 weeks of treatment were required before positive results were observed. Many questions remain unanswered about Ginkgo biloba including long-term efficacy and toxicity and whether therapy should be intermittent or lifelong.²¹

Few adverse effects have been reported with Ginkgo biloba extract. The most frequent side effects reported are headache, hypersensitivity reactions and gastrointestinal upset. Diarrhoea, nausea and vomiting occurred in less than 1% of patients in clinical trials.^{3,18,21,24} Little information is available on the drug interaction profile of Ginkgo biloba extract.^{18,24} However since Ginkgo biloba inhibits PAF aggregation which may prolong bleeding time, combining it with drugs or herbs that have anticoagulant or antiplatelet effects warrants caution.²¹ Because of the effect on the arachidonic acid pathway the use of Ginkgo biloba extract during pregnancy should not be recommended.^{8,21}

Echinacea

Echinacea is a perennial herb with 9 species, all indigenous to the USA.²⁵ The chemistry of echinacea is complex and it is unclear which of the chemical constituents of the plant are responsible for pharmacological activity.²⁵ There are three general classes of compounds believed to exhibit non-specific immunostimulatory activity; the alkylamides, the chicoric acids and related glycosides and the high molecular weight polysaccharides.²⁵ Echinacea has been used in the prophylaxis and treatment of viral upper respiratory tract infections and as an adjunct to antimicrobial treatment in more severe infections. There are also reported uses for eczema, psoriasis and wound healing.^{8,12,26,27} Echinacea's immunostimulatory effects are nonspecific and primarily affect cell mediated immunity. Proposed mechanisms of action include activation of phagocytic macrophages, T lymphocytes and natural killer cells.²⁶

Echinacea is usually taken as an alcoholic extract in a liquid form or incorporated in the dry state into capsules or tablets.²⁷ Although the herb is extremely popular in Europe and the USA, well designed, double-blind, placebo-controlled studies are scarce. A small number of studies have shown a reduction in incidence, severity and duration of viral symptoms, but the study samples were small.²⁶

Echinacea has been reported to be relatively free of adverse effects. Mild allergic reactions have been reported with more severe allergic reactions including dyspnoea and anaphylaxis reported in patients with a history of asthma, atopy or allergic reactions.²⁶ Patients with a history of allergy to plants of the Asteraceae family e.g. sunflowers, chrysanthemums should be advised against using echinacea.²⁵ Echinacea should not be used in progressive systemic disorders such as multiple sclerosis, HIV infection and AIDS related illnesses.^{12,18} Limited information is available with regard to the drug interaction profile of echinacea. An antagonistic interaction between echinacea and immunosuppressive agents is possible. Increased bleeding time but not

necessarily an increased INR has been reported anecdotally for patients on long-term warfarin therapy.²⁶ There is currently no echinacea preparation with a product authorisation available in Ireland.

Ginseng

Ginseng comprises a number of different species which belong to the Araliaceae (ivy) family.²⁸ Korean, Japanese and American ginseng are of the genus *Panax* while Siberian ginseng is of the genus *Eleutherococcus*.²⁹ Several active substances are present including ginsenosides in *Panax* species and eleutherosides in *Eleutherococcus* species.³⁰ There are several preparations of ginseng available with product authorisations in Ireland.

Ginseng is claimed to be an adaptogen i.e. it increases the body's resistance to stress and builds up general vitality. To date it has been used primarily to prevent fatigue or infection and as a tonic in convalescence or general exhaustion. It enjoys a widespread reputation as an aphrodisiac but this action is not supported in the historical or scientific literature.²⁸ Traditionally ginseng use has been divided into short-term use - to improve stamina, concentration, healing process and work efficiency in healthy individuals and long-term use - to improve the well-being in debilitated and degenerative conditions especially those associated with old age.⁸

Side effects reported with ginseng use include transient nervousness, excitation, insomnia, inability to concentrate, headache, hypertension, epistaxis and allergies. Ginseng may also produce an oestrogen like effect manifesting as mastalgia and vaginal bleeding as reported in elderly postmenopausal women taking a modest oral dose.³⁰ Ginseng is not indicated for use in children and healthy adults under 40. It is not recommended for use in pregnant women, hypertensives or diabetics.²⁸ Ginseng Abuse Syndrome resulting from the ingestion of large doses of ginseng, has been reported to occur with long-term use of ginseng. Symptoms include hypertension, nervousness, sleeplessness, skin eruptions and morning diarrhoea.^{28,30} The study which led to these conclusions has been criticised and the existence of this syndrome has now been questioned.²⁸ With regard to drug interactions there is some evidence that interactions may occur between ginseng and steroidal drugs. Enhancement of the effect of hypoglycaemic drugs may also occur.²⁸

In conclusion, the use of herbal medicinal products has increased dramatically in the last number of years and is likely to continue to do so. At present there is limited evidence of efficacy in the form of well-designed clinical trials. Without mandatory quality control or adequate post-marketing surveillance clinicians should continue to be aware of the expected and unexpected effects of herbal products.

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