St John’s wort
(Hypericum perforatum L.)

SYNONYMS
Hypericum, hardhay (Engl), Hyperici herba (Lat), Johanniskraut, Sonnenwendkraut, Hartheu (Ger), herb de millepertuis (Fr), iperico (Ital), prikbladet perikon (Dan).

WHAT IS IT?
The dried aerial parts of Hypericum perforatum, gathered during the flowering period or shortly before, are used medicinally. The generic name of the herb derives from the Greek meaning to ‘overcome an apparition’ and in earlier times homes would have a plant hanging over the door to ward off evil spirits. This species of hypericum (H. perforatum) is referred to as perforate St John’s wort due to the perforated appearance of the leaves when they are held up to the light. H. perforatum is not a weed in its native Europe, Asia and North Africa but has become a weed in most temperate regions of the world. Hypericum and other species of the genus have been used as a remedy since ancient times particularly to treat ulcers, burns, wounds, abdominal pains and bacterial diseases. Recently it has received attention in clinical trials for the treatment of depression and viral diseases.

EFFECTS
Mild antidepressant activity; useful for wound healing; antiviral activity with application to disorders caused by enveloped viruses.

TRADITIONAL VIEW
Hypericum was considered primarily for the nervous system, particularly for nervous affictions (excitability, menopausal neurosis, hysteria) and disorders of the spine, spinal injuries, neuralgia, sciatica and muscular rheumatism. It was also used for its supposed diuretic and astringent properties and to treat urinary problems, diarrhoea, dysentery, parasitic infestations, jaundice, haemorrhages, menorrhagia and bed wetting. Hypericum ointment and infused oil were used on a wide range of wounds including ulcers, swellings, bruises and even on tumours. In Greece the herb is used externally for the treatment of shingles.

SUMMARY ACTIONS
Antiviral, nerve, antidepressant, vulnerary, antiseptic.

CAN BE USED FOR
INDICATIONS SUPPORTED BY CLINICAL TRIALS
Treatment of mild to moderate depression, particularly when side effects from standard antidepressant drugs become intolerable to the patient; adjunct to standard drug treatment in severe depression; treatment of anxiety; adjunct to light therapy for seasonal affective disorder; psychological symptoms of menopause; aerobic endurance in athletes.

TRADITIONAL THERAPEUTIC USES
Physiological afflictions of the nervous system: spinal injuries, neuralgia, sciatica; muscular rheumatism; mild psychological disorders: excitability, menopausal anxiety and nervousness. Hypericum ointment and infused oil for the treatment of wounds, bruises and shingles.

MAY ALSO BE USED FOR
EXTRAPOLATIONS FROM PHARMACOLOGICAL STUDIES
Treatment and prevention of acute and chronic infections caused by enveloped viruses, e.g. cold sores, herpes genitalis, chicken pox, shingles, glandular fever, cytomegalovirus infection and viral hepatitis; wound healing; conditions requiring increased nocturnal melatonin plasma levels (e.g. circadian rhythm-associated sleep disorders); alcoholism; may also have potential as an anticancer treatment.

OTHER APPLICATIONS
Inclusion in skin care products, particularly for sensitive skin.

PREPARATIONS
Dried or fresh herb for infusion, liquid extract and tablets for internal use.

Infused oil of hypericum is made by mixing the flowers in a good-quality fixed oil (such as olive oil) in
a well-sealed vessel in the presence of sunlight over several weeks. The action of the sunlight produces a red oil containing hypericin derivatives, hyperforin, xanthones, flavonoids and the breakdown products of hyperforin.

**DOSAGE**

- 2–5 g of dried herb per day or the equivalent of 1.0–2.7 mg of total hypericin (TH) per day.
- Hypericum tablets (1.5 g, standardized to contain 0.9 mg TH): 2–3 tablets per day.
- The volume of liquid extract prescribed depends upon the level of TH in the extract; typical doses are 3–6 ml of 1:2 liquid extract per day, 7.5–15 ml of 1:5 tincture per day.

Doses at the higher end of this range have been utilized in the treatment of depression, HIV infection and other viral infections. For the short-term treatment of acute viral infections, even higher doses may be necessary.

**DURATION OF USE**

No restriction but at least 4 weeks of treatment is required to assess the antidepressant effect. (See the Special warnings section.)

**SUMMARY ASSESSMENT OF SAFETY**

A scientific investigation found that use of hypericum extract is safer for patients with preexisting cardiac dysfunction or elderly patients than tricyclic antidepressants. Adverse effects are rare from the use of hypericum at normal dosages. Avoidance of excessive exposure to sunlight or artificial UVA light is advisable in patients taking high doses. Hypericum should be used cautiously in patients with known photosensitivity. Practitioners should avoid dispensing the sediment from hypericum extracts. (Refer to Side effects section.)

**TECHNICAL DATA**

**BOTANY**

Hypericum is a member of the Clusiaceae (alternative name: Guttiferae) family and grows to approximately 1 m with opposite and paired branches. The leaves are opposite, sessile, up to 2 cm long, oblong and contain numerous translucent glandular dots which are visible against the light. The yellow flowers contain five petals with many stamens protruding. The fruit is a capsule.

**KEY CONSTITUENTS**

- Naphthodianthrones (0.05–0.6%), including hypericin and pseudohypericin. The upper level of naphthodianthrones is usually much lower than this quoted value, approximately 0.2%.
- Flavonoids, phenolics including hyperforin, procyanidins, essential oil.

Collectively the naphthodianthrones, hypericin (H) and pseudohypericin (PH) are called ‘total hypericin’ (TH) and are responsible for the red colour of hypericum extracts. The naphthodianthrones show a restricted solubility in almost all solvents, but more than 40% of the amount present is extractable from the crude herb when preparing a tea with water at 60–80°C. This increase in solubility suggests the possible presence of factors in the herb which modify the solubility of the naphthodianthrones. Accordingly, potassium salts of H and PH have been identified as ‘soluble’ pigments in Hypericum species.

**PHARMACODYNAMICS**

**Antiviral and antiretroviral activity**

Hypericin and PH have demonstrated activity against several enveloped viruses in vitro, including vesicular stomatitis virus, herpes simplex virus types 1 and 2, parainfluenza virus, vaccinia virus, murine cytomegalovirus and duck hepatitis B virus. These compounds were inactive against non-enveloped (naked) viruses such as human rhinovirus, adenovirus and poliovirus. This suggests that the mechanism of viral inactivation is dependent upon the presence of a viral lipid envelope. The antiviral activity was enhanced by exposure to light and is directed at both the virions and virus-infected cells. Hypericin and PH appear to inactivate the viral fusion function via the generation of singlet oxygen upon illumination which could also occur in vivo in the absence of light if driven by chemically generated excited states. Hypericin and PH also interfere with more than one stage in the virus replication cycle (see also below). Both H and PH demonstrated potent activity, in vitro and in vivo (by oral administration or injection) against several retroviruses, including HIV. The antiretroviral activity was enhanced by exposure to light. The ring structure, the quinone and phenolic groups are necessary for the antiretroviral activity.

The antiretroviral effect is postulated to be achieved in a number of ways:

- by causing photochemical alterations of the capsid, which inhibits the release of reverse transcriptase
and prevents reverse transcription of the genome within the target cell;\textsuperscript{20}

• by inhibiting intracellular transmission of the HIV-induced cytopathic signal;\textsuperscript{25,26}

• by interfering with processing of gag-encoded precursor polypeptides needed for core maturation;\textsuperscript{22}

• by impairing the assembly or processing of intact virions;\textsuperscript{22}

• by inhibiting the signalling pathway which has an immunosuppressive effect on the host immune system.\textsuperscript{27}

The antiretroviral activity is due to a combination of the photodynamic and lipophilic properties of these compounds: H binds cell membranes and crosslinks virus capsid proteins which results in a loss of infectivity and an inability to retrieve the reverse transcriptase activity from the virion.\textsuperscript{28}

### Antidepressant activity

Information from in vitro studies on key constituents is inconclusive. Hypericin extract and H inhibited dopamine-beta-hydroxylase in vitro.\textsuperscript{29} Hypericin also potentiated neurotransmitter binding at the GABA-A, benzodiazepine and serotonin receptors.\textsuperscript{30} The non-hypericin fraction of hypericum inhibited monoamine oxidase-A (MAO-A) in vitro, unlike H and the flavonoids.\textsuperscript{31,32} The xanthones, flavones and flavonols were found to be potent and selective MAO-A inhibitors and the coumarins affected MAO-B in vitro.\textsuperscript{32} Amentoflavone demonstrated binding activity at the benzodiazepine receptor in vitro.\textsuperscript{33} One group of researchers have suggested, on the basis of their in vitro and in vivo studies, that hyperforin significantly contributes to the antidepressant activity.\textsuperscript{34,35} More investigation is required into the role that hyperforin might play in the antidepressant activity of hypericum.

Studies on the whole extract of hypericum have revealed the following results which may reflect on antidepressant activity.

• Inhibition of synaptic uptake of noradrenaline, serotonin and dopamine in vitro and inhibition of GABA reuptake.\textsuperscript{36,37,38} It is unusual to find this action on all three uptake systems.\textsuperscript{38}

• Downregulation of beta-adrenoceptor density in the frontal cortex after subchronic administration in vivo.\textsuperscript{36,38,39} (Note: The downregulation of these receptors in vivo is expected on subchronic administration of antidepressants and is not in contradiction to inhibition of uptake observed in vitro.)

• Upregulation of central serotonergic receptors from cerebral tissue in vivo, which is consistent with effects caused by synthetic antidepressants.\textsuperscript{36,40}

• Reduced expression of serotonin receptors in vitro.\textsuperscript{41}

• Inhibition of catechol-O-methyltransferase in vitro.\textsuperscript{42}
could be linked to antidepressant activity. These changes could be linked to antidepressant activity.

- Inhibition of MAO-A and MAO-B activity in vitro, although this inhibition was found to be weak.
- A photosensitizing effect for H, since hypericum treatment has lowered the amount of light necessary to obtain a clinical antidepressant effect.

The relative significance of these in vitro and in vivo results to the mechanism behind the clinical antidepressant activity of hypericum is currently uncertain.

In further work to elaborate the components contributing to antidepressant activity, the antidepressant activity of the clinically proven 80% methanolic extract of hypericum and its various fractions was tested using the forced swimming test and tail suspension test in rats. Fraction II (containing flavonoids) and fraction IIc (containing procyanidins, H and PH) were determined to contribute to the observed in vivo antidepressant activity. Procyanidins in fraction IIc significantly increased the in vivo effects of H and PH, probably by a solubilizing effect (these compounds otherwise have poor solubility). The effect of solubilized H and PH was antagonized by a dopamine antagonist, suggesting that the dopaminergic system is involved in their action. Hyperforin could not be found in any of the six fractions, presumably because it is unstable. Although this research verifies that H and PH do have experimental antidepressant activity, it should not be interpreted that they are the only compounds with such activity in hypericum.

In a placebo-controlled, two-way crossover trial on 12 healthy volunteers, 6 weeks of hypericum treatment (1.1 mg per day TH equivalent) induced significant differences in EEG patterns. The changes were typical of those induced by antidepressant drugs such as imipramine. In a double-blind, crossover, placebo-controlled study over 4 weeks on 12 older healthy volunteers, hypericum extract (2.7 mg per day TH equivalent) induced an increase in deep sleep during the total sleeping period, as evidenced by EEG and visual analysis. The interference with REM sleep phases which is typical for tricyclic antidepressants and MAO inhibitors did not occur for hypericum. Continuity of sleep, onset of sleep, intermittent wake-up phases and total sleep duration were not improved by hypericum, which implies it does not exert sedative activity.

One hundred and sixty patients suffering from depression completed a randomized, double-blind, multicentre study investigating the electrocardiographic (ECG) effects of high-dose hypericum treatment (1800 mg extract, 5.4 mg TH) compared to imipramine. Analysis of conduction intervals and pathological findings indicated that, for the treatment of patients with a preexisting conductive dysfunction or elderly patients, high-dose hypericum extract is safer with regard to cardiac function than tricyclic antidepressants.

**Anticancer activity**

Hypericum has produced a potent antitumour activity in vitro against several tumour cells. However, it did not show any toxic effect on normal cells at much higher concentrations. Based on additional experiments it was concluded that H directly inhibits EGF-receptor and PTK activity. Epidermal growth factor (EGF) is a cellular plasma membrane receptor which appears to be involved in the loss of inhibitory constraint on cell growth, a factor in tumour formation. Phosphorylation of proteins on tyrosine residues is a key biochemical reaction that mediates a large variety of cellular signals, including control of the cell cycle and cell differentiation. Enhanced protein tyrosine kinase (PTK) activity is also involved in the transformation of normal cells into tumour cells.

It is premature to conclude that H or hypericum is an effective antiproliferative agent against tumour cells. However, this research looks promising from at least a pharmacokinetic perspective. Concentrations of about 0.3 μM were effective against human colon and stomach cancer cell lines and mouse leukaemia cells. Pharmacokinetic experiments on hypericum extract show that a dose containing 11.25 mg of TH gives a maximum plasma concentration 4 hours later of about 0.3 μM. (Refer to the Pharmacokinetics section below.)

In vitro studies demonstrated a large difference in sensitivity for tumour cell lines towards photo-activated H. Hypericin also demonstrated antitumour activity in vivo after intraperitoneal injection.

An antimutagenic activity was demonstrated by hypericum extract on DNA repair in *Escherichia coli*. Hypericin also reduced the activity of UV-induced beta-galactosidase, indicating that the antimutagenic activity may be due to suppression of error-prone repair.

**Other activity**

Hypericum extract demonstrated bactericidal activity in vitro against a number of Gram-positive and Gram negative bacteria, including *Staphylococcus aureus*,...
Hypericin and PH are well absorbed into the bloodstream after oral doses of hypericum extract. In pharmacokinetic studies, after hypericum administration to volunteers, H showed better total absorption than PH although PH was more quickly absorbed. Over 14 days of treatment with a standardized hypericum extract in 13 healthy volunteers, steady-state levels of H and PH in blood plasma were reached after 7 and 4 days respectively. The systemic availability of H and PH in the extract was roughly estimated to be 14% and 21% respectively. In a single-dose, double-blind study, 13 volunteers received placebo or the following dose of standardized hypericum extract: 900 mg (equivalent to 2.81 mg of TH), 1800 mg (equivalent to 5.62 mg of TH) or 3600 mg (equivalent to 11.25 mg of TH). Approximately 4 hours after intake, maximum TH plasma concentrations were 0, 0.028, 0.061 and 0.159 mg/l respectively. Because of their fat-loving nature, H and PH move readily throughout the body and across the blood–brain barrier.

CLINICAL TRIALS

Antiviral and antiretroviral activity

In the first reported case studies of HIV-positive patients who had been taking hypericum preparations (0.35–1.2 mg TH per day), nine (of 11) patients demonstrated successful treatment as evidenced by symptomatic relief of fatigue, nausea, mild peripheral neuropathies and abatement of swollen lymph glands. Changes in CD4 cell counts and p24 antigen levels occurred in five patients, which returned to baseline after 1 month without hypericum.

In an ongoing uncontrolled trial, 16 HIV patients at various stages of the disease process were treated by intravenous injection and oral route with hypericum. Over 40 months of observation, patients showed stable or increasing CD4 cell counts and only two patients encountered an opportunistic infection. None of the known viral complications due to cytomegalovirus, herpes or Epstein–Barr virus were encountered.
There were no cases of toxoplasmosis, neurological symptoms or photosensitivity. A substantial decline in viral load was observed in most of the 18 AIDS patients undergoing a similar treatment regime (intravenous injection and oral hypericum) for 4–6 years. In those patients who experienced an increase in viral load, there was no effect on the clinical outcome of viral cytomegalovirus, herpes or Epstein–Barr virus complications.

Twenty-four HIV-infected patients in Thailand participated in a study to determine the maximum tolerated effective oral dose (MTD) of H which demonstrates antiviral activity with minimal phototoxic effects. The MTD was found to be 0.05 mg/kg. In a toxicological study involving 10 HIV-positive homosexual men, daily dosages of 0.5, 2.0 4.0 and 8.0 mg H were each administered for 12 weeks. No early, marked anti-HIV activity was found. There have also been two phase I/II studies of synthetic H in HIV-infected subjects, investigating phototoxicity, pharmacokinetics and antiviral activity by oral or intravenous administration. A consistent change in antiviral endpoints was not seen with intermittent intravenous dosing. Pharmacokinetic data indicated that chronic oral dosing would achieve sustained blood levels in an antiretroviral range.

**Antidepressant and antianxiety activity**

Many clinical trials have been conducted over the past 17 years, using some form of standardized hypericum extract (equivalent to 0.4–2.7 mg TH per day). There has been a tendency in later years to use higher doses of TH (2.7 mg per day, about 5 g of herb) and recently even 5.4 mg per day.

Many criticisms have been levelled at the trials conducted from 1979 to 1995 including:

- few trials conducted on severe depression;
- relapses occurring within 1 year after cessation of the studies were not registered;
- dose-response studies were not performed with patients;
- in trials comparing standard antidepressant medications, the doses were too low and the number of patients too small;
- drug interactions were not specifically tested;
- special groups of patients (e.g. geriatric patients, those with renal and hepatic insufficiencies) were not tested.

A critical analysis of 23 randomized clinical trials including a total of 1757 outpatients has shown that hypericum extracts are more effective than placebo for the treatment of mild to moderately severe depressive disorders. Fifteen trials with 1008 patients were placebo controlled and eight with 749 patients compared hypericum to standard antidepressant drugs (maprotiline, imipramine, bromazepam, amitriptyline, desipramine). Of the eight trials comparing hypericum with other antidepressants, six used single preparations and two used a combination of hypericum and valerian. Three of the trials used hypericum in combination with other plant extracts, one trial was single blind, two were open and the remainder were double blind. Most trials had reasonably good methodology, with 10 trials scoring 80% or more of the possible points in both assessment systems used. The daily dose of TH varied considerably, between 0.4 and 2.7 mg, as did the duration of treatment (2–12 weeks).

Hypericum extracts were significantly superior to placebo, with mean scores on the Hamilton Depression Scale 4.4 points better for patients treated with hypericum (in the nine trials providing data for analysis). Results from comparative trials suggest that hypericum may work as well as standard antidepressants, as indicated by the scores on the Hamilton Depression Scale after treatment. In these trials with standard antidepressants, however, the evidence was insufficient to form definite conclusions due to the limited number of patients included in the trials. In the six trials comparing single hypericum preparations with standard antidepressants, side effects occurred in 20% of patients taking hypericum extracts compared to 36% of patients on standard antidepressants. The authors conclude that further studies are required, with the type of depression among study participants better delineated. They also suggested that comparison of studies using different preparations of hypericum is problematic, even when standardized for TH, as the preparations may vary in other substances contributing to the antidepressant effect.

Clinical trials on hypericum which were not included in the above review and metaanalysis are reviewed below.

In a randomized, multicentre, double-blind trial, 209 patients diagnosed with recurrent severe major depression received either hypericum extract (5.4 mg per day TH equivalent) or 150 mg of imipramine over 6 weeks. Both treatments were found to be equally effective in improving symptoms of severe depression but the decrease in depressive symptoms tended to be greater for imipramine. Even at the higher dose hypericum was better tolerated than imipramine, as evidenced by fewer patients reporting adverse effects and fewer dropouts (one dropout versus eight). There were no reports of photosensitivity. This trial is significant
because patients had severe depression and the doses of hypericum and imipramine were both relatively high.

In a randomized, multicentre, double-blind trial, 149 patients with mild to moderate depression received hypericum extract (2.7 mg per day TH equivalent) or amitriptyline over 6 weeks. Comparable efficacy was observed between the two treatments for final Hamilton Depression Scores and global clinical impression. The mean rating scales at the end of the trial favoured amitriptyline. A lower incidence of side effects occurred in the hypericum group.103 In a randomized, double-blind trial, 102 outpatients with mild to moderate depression received either hypericum extract (2.7 mg per day TH equivalent) or placebo. The placebo group also responded favourably when switched to active treatment for 2 weeks. The total Hamilton score in the hypericum treatment group fell significantly (p<0.001) further after 4 weeks than in the placebo group.101

In a preliminary single-blind trial, 20 patients with seasonal affective disorder (SAD) were randomized to receive hypericum extract (2.7 mg per day TH equivalent) combined with either bright or dim light therapy for 4 weeks. A significant reduction of Hamilton Depression Scores was observed in both light groups, with no significant difference between the two groups. The favourable response in the dim light group suggests hypericum may be an efficient therapy in patients with SAD, as well as in combination with light therapy.102 In another similar single-blind trial, 4 weeks’ treatment with hypericum extract (2.7 mg per day TH equivalent) was associated with a significant reduction in the total Hamilton score. There was no significant additional advantage for bright light treatment over hypericum.103

The effectiveness of hypericum treatment was assessed by 663 medical practitioners in a postmarketing surveillance study of 3250 patients with depressive tendencies. Patients received hypericum extract (2.7 mg per day TH equivalent) for 4 weeks. At the end of treatment, of the 3161 patients remaining in the trial, 79% of patients and 82% of doctors assessed the results as between ‘better’ and ‘symptom free’ and 13–16% evaluated results as either ‘unchanged’ or ‘worse’. Patients with light or moderate depression responded better to treatment than those with severe depression.104

The safety and efficacy of two hypericum extracts (standardized to 0.5% and 5.0% hyperforin respectively) were compared in 147 patients with mild to moderate depression in a randomized, double-blind, placebo-controlled trial.105 After 6 weeks of treatment, only the group taking the 5.0% hyperforin extract showed a significant reduction for the Hamilton Depression Score when compared to placebo (p=0.0004). This study suggests an antidepressant activity for hyperforin, which is not usually present in conventional hypericum extracts.47

From the clinical trials performed between 1993 and 1996 and subsequently, it can be concluded that hypericum is a well-tolerated and effective alternative to standard antidepressants in the treatment of mild to moderate depression, particularly when side effects with the drugs become intolerable to the patient. Patients should be treated long enough and with a sufficiently high daily dose of at least the equivalent of 2.7 mg TH from hypericum extracts.74

**Other activity**

An open, multicentre, postmarketing surveillance study investigated the efficacy and tolerance of a combination of hypericum and black cohosh in the treatment of 812 patients for psychological complaints experienced in menopause. Good improvement was observed in 90% of patients, with improved concentration and reduction in hot flushes. The treatment demonstrated an effect after 3 weeks, with 2% of patients experiencing side effects (most frequently gastrointestinal complaints).106

In a double-blind placebo-controlled trial, 72 athletes were randomized into three groups: hypericum plus vitamin E, vitamin E and placebo. The daily dose of hypericum used in the above study was around 170 mg of standardized extract, probably corresponding to about 1 g of dried herb. Measurements of endurance capacity and physical comfort were conducted at 0, 3 and 6 weeks. After 6 weeks, the hypericum plus vitamin E group demonstrated a better aerobic endurance capacity (p=0.006) compared to little significant change in the other groups.107 The trial design does not permit the conclusion that hypericum alone enhances physical endurance (it may only act in this way when combined with the vitamin E and minerals). The daily dose of vitamin E used in the trial was 660 mg.

Phase I/II clinical trials of an oral H formulation for glioblastoma and a topical, light-activated formulation for skin diseases such as psoriasis are continuing.108

**TOXICOLOGY**

Hypericum has very low toxicity. Animals given 2 g/kg per day of dried hypericum for up to a year showed no signs of any toxic changes.109,110

Hypericum is a state of sensitivity to sunlight following the ingestion of large quantities of hypericum. When plants are eaten by livestock, weakly pigmented parts of the body become affected by a type of
dermatitis. This is due to TH, which causes photosensitivity without jaundice and there is no liver damage. Sheep, cattle, horses and goats are affected, with goats the most resistant. The disorder depresses the central nervous system and causes increased sensitivity to handling and temperature change. A review of the effect of hypericum on grazing animals notes that hypericum is more phototoxic if ingested at flowering than when young or dry. The minimum phototoxic dose of foliage for cattle and sheep is approximately 1% and 4% of live weight respectively (i.e. 10 and 40 g/kg). Doses of 3 g/kg or more of ground, dried hypericum aerial parts, given by stomach tube, were able to photosensitize 4–6-month-old calves.

Hypericum given to animals (1–1.5 g/kg per day) did not adversely affect the health of the foetus or of the mother. The fertility of adult animals was not affected. Genotoxicity tests showed no mutagenic effects following hypericum administration. CONTRAINDICATIONS

Hypericum is a safe and effective alternative to orthodox antidepressants in the treatment of mild to moderate depression. But it is not suited for the treatment of serious depression with psychotic symptoms, suicidal risk or signs and symptoms that are so severe that they do not allow the patient’s family or work involvement to continue. However, in these cases, hypericum may be a valuable adjunct to other therapy such as drug therapy and psychotherapy.

SPECIAL WARNINGS AND PRECAUTIONS

Hypericum is not advisable in cases of known photosensitivity. (Refer to the Side effects section.) It is recommended that patients on higher doses of hypericum (2.7 mg or more of TH equivalent per day) do not spend excessive amounts of time in the full sun, especially in tropical or subtropical climates, and avoid artificial UVA irradiation. However, total avoidance of sunlight is not advisable because the activity of hypericum may be associated with its photosensitizing activity. Avoidance of foods which interact with MAO-inhibiting drugs, such as tyramine-containing foods (cheeses, beer, wine), and drugs such as L-dopa is not necessary. If a significant response in depressive disorders is not apparent after 4–6 weeks, the treatment should be discontinued.

INTERACTIONS

Negative interactions are not expected. In fact, several cases have been reported indicating a favourable interaction of hypericum with orthodox medication in severe depressive states. However, caution should always be exercised in patients consuming orthodox medication. Patients should be monitored for any symptoms suggestive of serotonin syndrome (such as confusion, fever, shivering, sweating, diarrhoea and muscle spasms). Serotonin syndrome is an adverse drug interaction characterized by altered mental status, autonomic dysfunction and neuromuscular abnormalities. It is most frequently caused by the use of selective serotonin reuptake inhibitors (SSRI) and MAO inhibitors, leading to excess serotonin availability in the CNS at the serotonin 1A receptor.

A case of suspected serotonin syndrome has recently been reported. The 50-year-old woman had stopped taking paroxetine 10 days prior to commencing hypericum (600 mg per day). After this short space of time taking hypericum, she restarted the paroxetine to assist her sleep. The following day she experienced lethargy and grogginess. The author postulated that an adverse reaction occurred between the SSRI (paroxetine) and hypericum. However, the evidence for this conclusion is not strong. A yet-to-be-published study describes two patients who developed what appeared to be classic serotonin syndrome. The syndrome developed in one patient who took hypericum alone and was seen in another patient who took hypericum and trazodone (a weak SSRI) 6 days after the patient stopped taking the SSRI. The authors indicate that it is not clear whether the hypericum caused the serotonin syndrome, the trazodone the one patient was taking, or the combined effect.

USE IN PREGNANCY AND LACTATION

No data available. The scientific committee of ESCOP suggests that in accordance with general medical practice, the product should not be used during pregnancy and lactation without professional advice.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No negative influence is expected.

SIDE EFFECTS

General

In HIV-positive patients receiving oral hypericum extracts containing the equivalent of 1 mg H per day, mild reversible liver enzyme elevations were observed which returned to baseline levels after 1 month without hypericum.
In the postmarketing surveillance study of 3250 patients receiving hypericum extract (equivalent to 2.7 mg per day TH) for treatment of depression, 2.4% reported side effects (mainly minor gastrointestinal complaints and allergic reactions such as pruritus). The incidence of side effects with the hypericum preparation was estimated to be 10 times less than that experienced with orthodox antidepressants.104

A case of a dynamic ileus associated with the use of hypericum in a 67-year-old woman has been reported. Her symptoms started 2 weeks after taking the extract, with no other identifiable cause, and resolved gradually and completely after its discontinuation.116

Hypericism

There have been no reliable reported cases of hypericism in humans taking oral doses of hypericum. The usual therapeutic doses of hypericum extract are about 30–50 times below the dose needed to induce phototoxicity in calves.117 However, an oral dose of 0.05 mg/kg per day of pure hypericin over 28 days produced mild photosensitivity of a short duration on exposure to sunlight in three out of four HIV patients in a study in Thailand. When the dose was raised to 0.16 mg/kg, two patients developed intolerable symptoms of photosensitivity and the other developed mild symptoms.71

In a single-dose study, healthy volunteers received standardized hypericum extract (equivalent to 2.81, 5.62 or 11.25 mg of TH). No evidence of photosensitivity was observed when their skin was irradiated with both UVA and UVB light 4 hours later. Sensitivity to UVA light was increased only after the highest dose of extract. The results of a multiple-dose study using 1800 mg extract (equivalent to 5.62 mg of TH) over 15 days indicated that hypericum extract caused no significant change in UVB photosensitivity but a moderate increase in UVA photosensitivity. It was concluded that patients should reduce artificial UVA irradiation while taking hypericum, but normal doses of hypericum should represent no concern with regard to photosensitivity.18,53

Hypersensitivity reactions

There have been reports of an adverse reaction consisting of sensory nerve hypersensitivity occurring in patients consuming tablets and liquid extracts of hypericum in Australia and New Zealand in recent years. Based on the clinical experience of some Australian practitioners, there is evidence to suggest that these patients ingested hypericum preparations from late harvested herb which contained high levels of resinous constituents which would not normally be ingested, e.g. the sediment in a liquid extract. This can be avoided by not dispensing the sediment and by using hypericum harvested before or at the onset of full flowering. The hypersensitivity reaction was not hypericism.119

A possibly related case of subacute toxic neuropathy (nerve damage) has been reported. The woman began to experience sharp pains in areas exposed to the sun (face and hands) after 4 weeks’ treatment with an over-the-counter preparation of hypericum (500 mg, concentration undefined). Painful sensitivity on her arms and legs occurred after sunbathing. Her symptoms began to improve and eventually disappeared after she stopped using the product.120

OVERDOSE

Overdose with hypericum has not been reported. Phototoxicity could be expected to occur. Typical phototoxic symptoms include rash, pruritus and erythema 24 hours after exposure to ultraviolet light.

CURRENT REGULATORY STATUS IN SELECTED COUNTRIES

Hypericum became official in late 1998 in the United States Pharmacopeia-National Formulary (USP23–NF18, 1995–June 1999). Hypericum is covered by a positive Commission E monograph and can be used for psychogenic disturbances, depressive states and excitability. Infused oil of hypericum can be used internally for dyspeptic complaints and externally for the treatment of wounds, bruises, myalgia and first-degree burns. Hypericum is on the UK General Sale List.

Hypericum does not have GRAS status. However, it is freely available as a ‘dietary supplement’ in the USA under DSHEA legislation (1994 Dietary Supplement Health and Education Act). Hypericum has been present in OTC digestive aid drug products. The FDA, however, advises that: ‘based on evidence currently available, there is inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses’. Hypericum is also being combined with other constituents such as ma huang (Ephedra) and promoted for weight loss. The FDA has issued a warning that this treatment is not safe and/or effective.

Hypericum is not included in Part 4 of Schedule 4 of the Therapeutic Goods Act Regulations of Australia.
REFERENCES