St. John's Wort

Species (Family)

Hypericum perforatum L. (Hypericaceae)

Synonym(s)

Hypericum, Millepertuis

Part(s) Used

Herb

Pharmacopoeial and Other Monographs

American Herbal Pharmacopoeia[G1]
BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
ESCOP 1996[G52]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
USP24/NF19[G61]

Legal Category (Licensed Products)

GSL (for external use only)[G37]

Constituents[1,G1,G2,G22,G40,G48,G52,G62,G64]

Anthraquinone derivatives (naphthodianthrones) Hypericin, pseudohypericin and isohypericin; protohypericin and protopseudohypericin (biosynthetic precursors of hypericin and pseudohypericin, respectively) are present in fresh material. Cyclopseudohypericin is also stated to be present. The hypericin content (approximately 0.1–0.15%) includes both hypericin and pseudohypericin[2] and is sometimes referred to as 'total hypericins'.

Flavonoids Flavonols (e.g. kaempferol, quercetin), flavones (e.g. luteolin) and glycosides (e.g. hyperoside, isoquercitrin, quercitrin, rutin), biflavonoids including biapigenin (a flavone) and amentoflavone (a biapigenin derivative)[3,4] and catechins (flavonoids often associated with condensed tannins).[5,6] The concentrations of rutin, hyperoside and isoquercitrin have been reported as 1.6, 0.9 and 0.3%, respectively.[7]

Prenylated phloroglucinols Hyperforin (2.0–4.5%) and adhyperforin (0.2–1.9%).[5,8,9,G1]

Tannins 8–9%. Type not specified. Proanthocyanidins (condensed type) have been reported.[G2]

Other phenols Caffeic, chlorogenic, *p*-coumaric, ferulic, *p*-hydroxybenzoic and vanillic acids.

Volatile oils 0.05–0.9%. Major component (not less than 30%) is methyl-2-octane (saturated hydrocarbon); others include *n*-nonane and traces of methyl-2-decane and *n*-undecane (saturated hydrocarbons),[10] α- and β-pinene, α-terpineol, geraniol, and traces of myrcene and limonene (monoterpenes), caryophyllene and humulene (sesquiterpenes).[11,12]

Other constituents Acids (isovalerianic, nicotinic, myristic, palmitic, stearic), carotenoids, choline, nicotinamide, pectin, β-sitosterol, straight-chain saturated hydrocarbons (C_{16}, C_{30})[10,13] and alcohols (C_{24}, C_{26}, C_{28}).[10,13]

Food Use

St. John's wort is listed by the Council of Europe as a natural source of food flavouring (herb: category 5) (*see* Appendix 23).[G17]

Herbal Use[G1,G2,G7,G32,G64]

St. John's wort is stated to possess sedative and astringent properties. It has been used for excitability, neuralgia, fibrositis, sciatica, wounds, menopausal neurosis, anxiety and depression and as a nerve tonic. St. John's wort is used extensively in homeopathic preparations as well as in herbal products. Modern interest is focused on its use as an antidepressant.

Dosage

Dried herb 2–4 g or by infusion three times daily.[G7]

Liquid extract 2–4 mL (1 : 1 in 25% alcohol) three times daily.[G7]

Tincture 2–4 mL (1 : 10 in 45% alcohol) three times daily.[G7]

The doses of St. John's wort extract used in clinical trials involving patients with mild to moderate depression generally range from 350 to 1800 mg daily (equivalent to 0.4 to 2.7 mg hypericin daily, depending on the extract).[14]

Pharmacological Actions

The major active constituents are considered to be hyperforin (a prenylated phloroglucinol) and hypericin (a naphthodianthrone), although other biologically active constituents, e.g. flavonoids and tannins, are also present.[15] Several pharmacological activities, including antidepressant, antiviral and antibacterial effects, have been documented for extracts of St. John's wort and/or its constituents. The pharmacology and pharmacodynamics of St. John's wort have been reviewed.[1,16,G1,G50,G55]

In vitro and animal studies

Antidepressant activity The precise mechanism of action for the antidepressant effect of St. John's wort is unclear. Initially, attention was focused on hypericin as the constituent of St. John's wort believed to be responsible for the herb's antidepressant effects. Inhibition of monoamine oxidase (MAO) type A and B in rat brain mitochondria *in vitro* was described for hypericin.[17] However, other studies have demonstrated only weak or no MAO inhibition.[18–20]

In vitro receptor binding and enzyme inhibition assays carried out using hypericum extract demonstrated significant receptor affinity for adenosine, $GABA_A$, $GABA_B$, benzodiazepine and MAO types A and B, although, with the exception of $GABA_A$ and $GABA_B$, the concentrations of hypericum required were unlikely to be attained after oral administration in humans.[21] Other biochemical studies have reported that the hypericum extract LI 160 is only a weak inhibitor of MAO-A and MAO-B activity, but that it inhibits the synaptosomal uptake of serotonin (5-hydroxytryptamine or 5-HT), dopamine and noradrenaline (norepinephrine) with approximately equal affinity and also leads to a downregulation of β-receptors and an upregulation of 5-HT_2 receptors in the rat frontal cortex.[22] The effects of fluoxetine and hypericin- and flavonoid-standardised hypericum extracts (LI 160, 0.3% hypericin and 6% flavonoids and Ph-50, 0.3% hypericin and 50% flavonoids) on the concentrations of neurotransmitters in brain regions were studied in rats.[23] All three preparations induced a significant increase in 5-HT concentrations in the rat cortex, both LI 160 and Ph-50 caused increases in noradrenaline (norepinephrine) and dopamine in the rat diencephalon and Ph-50 also induced an increase in the noradrenaline (norepinephrine) content in the brainstem, areas that are implicated in depression.[23] In studies using the rat forced swimming test, an experimental model of depression, hypericum extracts induced a significant reduction in immobility.[24]

Hyperforin has now emerged as being one of the major active constituents of importance in antidepressant activity. Hyperforin has been shown to be an uptake inhibitor of 5-HT, dopamine, noradrenaline (norepinephrine), GABA and L-glutamate in synaptosomal preparations[25] and to inhibit 5-HT uptake in rat peritoneal cells in a dose-dependent manner.[26] Studies have also described discrepancies between observed and theoretical IC_{50} values, indicating that hyperforin is not the only component of hypericum extract that is responsible for the observed effects.[26,27] It has been reported that the mode of action of hyperforin in serotonin uptake inhibition seems to be associated with the elevation of free intracellular sodium ion concentrations[28] and that this may be secondary to activation of the Na^+/H^+ exchange as a result of a decrease in intracellular pH.[29] Hyperforin was shown to inhibit 5-HT reuptake in washed platelets but not in fresh platelet-rich plasma, suggesting that plasma-protein binding could be a limiting factor for 5-HT uptake inhibition *in vivo*.[30]

A commercial extract of St. John's wort has exhibited psychotropic and antidepressant activities in mice.[31] Pure hyperforin and hypericum extracts also demonstrated antidepressant activity in a despair behaviour test in rats.[26]

In other experimental models of depression, including acute and chronic forms of escape deficit induced by stressors, hypericum extract was shown to protect rats from the consequences of unavoidable stress.[32] Flavonoid fractions and flavonoids isolated from these fractions have been reported to have antidepressant activity in experimental studies (forced swimming test) in rats.[33]

Antimicrobial activity A leaf extract has been documented as enhancing the immunity of mice towards *Staphylococcus aureus* and *Bordetella pertussis*;[34] hyperforin is reported to be antibacterial with activity against *S. aureus*.[8] Antibacterial activity of hyperforin against multiresistant *S. aureus* and Gram-positive bacteria, including *Streptococcus pyogenes* and *Corynebacterium diphtheriae*, has been reported.[35] However, it has been emphasised that the antibacterial effects of hyperforin are only observed at high concentrations.[36,37] Hyperforin did not exhibit any growth inhibitory effect against Gram-negative bacteria, such as *Enterococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa* or

against *Candida albicans*.[35] Further antibiotic constituents have been isolated from St. John's wort: imanine and novoimanine.[38,39] Novoimanine was reported to be the most effective topical agent against *S. aureus*.[38] Herb extracts are reported to exhibit more pronounced activity against staphylococci, shigellae and *E. coli* than are decoctions.[39,40]

Antiviral activity Flavonoid and catechin-containing fractions have exhibited antiviral activity, inhibiting the influenza virus by 83–100%.[41] Hypericin and pseudohypericin have been reported to inhibit several encapsulated viruses *in vitro*, including herpes simplex types 1 and 2[42,43] and human immunodeficiency virus type 1 (HIV-1).[44–47] Hypericin has also been reported to inactivate murine cytomegalovirus (MCMV) and Sindbis virus.[47] The antiviral activity of hypericin appears to involve a photoactivation process.[47,G1]

Other effects *In vitro* studies using a hamster vas deferens smooth muscle cell line demonstrated that hyperforin induces the release of calcium ions from mitochondrial or other sources followed by activation of cellular metabolism.[48] It is not known whether this activity contributes to the antidepressant effects of hyperforin.

Oral administration of a single dose of St. John's wort (100, 200, 400, 600 or 800 mg/kg) to two strains of alcohol-preferring rats significantly reduced alcohol intake in both strains.[49] In another study in experimental alcoholism, acute intraperitoneal administration of St. John's wort (10–40 mg/kg), fluoxetine (1–10 mg/kg) and imipramine (3–30 mg/kg) reduced alcohol intake in a dose-dependent manner in a 12-hour, limited access, two-bottle choice (ethanol/water) procedure.[24] Depression and alcoholism are thought to have some neurochemical similarities, such as low brain serotonin concentrations.[50]

It has been suggested that biflavonoids may be the sedative principles in St. John's wort since CNS activity has been documented for biflavonoid constituents in another plant, *Taxus baccata*.[3]

An extract of St. John's wort was found to suppress inflammation and leukocyte infiltration induced by carrageenan and prostaglandin E_1 (PGE_1) in mice.[51] *In vitro*, hypericin has been shown to inhibit tumour necrosis factor-induced activation of the transcription factor NF-κB,[52] specific growth factor-regulated protein kinases[53–55] and the release of arachidonic acid and leukotriene B_4.[56] In a rabbit model of proliferative vitreoretinopathy (PVR), intravitreal injection of hypericin 0.1 mL (10 or 100 μmol/L, but not 1 μmol/L) inhibited the progression of PVR when compared with severity in control eyes five days after hypericin administration.[57] It was suggested that, as protein kinase C is important in the cellular reactions occurring in PVR, modulation of protein kinase C by hypericin may be a factor in this system. Hypericin and pseudohypericin have been reported to inhibit 12-lipoxygenase activity; the products of lipoxygenase-catalysed reactions, such as leukotrienes, may be involved in inflammatory reactions.[58]

Other compounds may contribute to the anti-inflammatory properties of St. John's wort.[37] Anti-inflammatory and anti-ulcerogenic properties have been documented for amentoflavone, a biapigenin derivative.[4] Analgesic activity in mice has been reported for the total flavonoid fraction;[59] the active principle was stated to be of the quercetin type.

Both water-soluble imanine and imanine were reported to reduce blood pressure and increase the frequency and depth of breathing following intravenous administration (50 mg/kg) to rabbits.[38] A study of the vasoconstrictor action of water-soluble imanine and imanine on the isolated rabbit ear indicated that their hypotensive action was not due to a direct effect on the vasculature.[38] When perfused through the isolated frog heart, both water-soluble imanine and imanine were found to cause cardiac systolic arrest at a dilution of 1×10^{-5}.[38] Proanthocyanidin-containing fractions isolated from St. John's wort have been reported to inhibit contractions of the isolated guinea-pig heart induced by histamine, $PGF_{2\alpha}$ and potassium chloride.[60]

A tonus-raising effect on isolated guinea-pig and rabbit uteri has been documented for a crude aqueous extract.[61] Of the group of plants investigated, St. John's wort was reported to exhibit the weakest uterotonic activity.

Tannins isolated from St. John's wort are stated to have mild astringent activity.[62] The anthraquinone derivatives documented for St. John's wort do not possess any purgative action.[G62]

In vitro cytotoxicity against human colon carcinoma cells (CO 115) has been described for hyperforin-related constituents isolated from *Hypericum calycinum* and *Hypericum revolutum*.[63]

Clinical studies

Clinical trials with extracts of St. John's wort have focused mainly on its effects in patients with depression, although there have been several studies exploring its use in other conditions, including seasonal affective disorder, chronic fatigue and premenstrual syndrome.

Depression Initially, hypericin was thought to be responsible for the antidepressant activity of St.

John's wort, although, more recently, experimental[25,26] and clinical evidence[64] has emerged to indicate that hyperforin is one of the major constituents required for antidepressant activity.

The precise mechanism of action of St. John's wort's antidepressant effect remains unclear (*see* Pharmacological Actions, *In vitro* and animal studies). A double-blind, placebo-controlled, crossover study in 12 healthy male volunteers investigated the effects of a single dose of St. John's wort extract (LI 160) (2700 mg, 9 × 300-mg tablets standardised to 0.3% hypericin) on plasma concentrations of growth hormone, prolactin and cortisol.[65] A significant increase in plasma growth hormone concentration and a significant decrease in plasma prolactin concentration were observed following St. John's wort administration relative to placebo administration. Plasma cortisol concentrations were unchanged. These findings suggest that this dose of St. John's wort extract may increase aspects of brain dopamine function in humans, although further studies are required to confirm this, assess dose–response relationships and determine whether there is evidence for effects on dopaminergic systems in patients with depression treated with St. John's wort.[65] Another study, which used a randomised, three-way, crossover design, investigated the effects of a single dose of St. John's wort extract (LI 160S) (600 or 300 mg) or placebo on hormone concentrations in 12 healthy male volunteers.[66] Compared with placebo, St. John's wort extract (600 mg) increased cortisol secretion between 30 and 90 minutes after dosing, indicating an influence of St. John's wort on certain CNS neurotransmitters. There was no difference between the three groups with regard to adrenocorticotrophic hormone (ACTH), growth hormone and prolactin secretion.[66]

A systematic review and meta-analysis of randomised controlled trials of preparations of St. John's wort extract included 23 trials involving a total of 1757 patients with depressive disorders.[67] This has been updated to include new studies and published as a Cochrane review of 27 randomised controlled trials of St. John's wort extract in patients with 'neurotic depression' and mild to moderately severe depressive disorders.[14] Seventeen of these trials (involving 1168 patients) compared St. John's wort preparations with placebo (16 studies used preparations containing St. John's wort extract as the sole herbal ingredient and one involved a combination product of St. John's wort extract with four other herbal ingredients); the ten other trials (involving 1123 patients) compared St. John's wort extracts with conventional antidepressant or sedative drugs, including amitriptyline, imipramine, desipramine and maprotiline (eight trials used single-ingredient preparations and two used combinations of St. John's wort and valerian). St. John's wort extracts were administered at doses ranging from 350 to 1800 mg; the hyperforin content of the preparations tested was not known. Most trials lasted for 4–6 weeks, although some studies were conducted for three months.

The results of the meta-analysis showed that St. John's wort preparations were significantly superior to placebo in the short-term treatment of mild to moderately severe depressive disorders (rate ratio 2.47 and 95% confidence interval (95% CI) 1.69–3.61). St. John's wort preparations were found to be as effective as conventional antidepressant agents (single preparations, rate ratio 1.01 and 95% CI 0.87–1.16), although for several reasons – for example, the use of low doses of conventional antidepressants and the trials involving small numbers of patients – this evidence was considered inadequate for establishing whether St. John's wort was as effective as conventional antidepressant drugs.[14] Further studies comparing St. John's wort preparations with standard antidepressant agents in well-defined patient groups and over longer periods were considered necessary.[14].

Another meta-analysis employed tighter inclusion criteria for trials in an effort to increase the validity of the analysis.[68] It included only randomised, blinded, controlled trials of St. John's wort as a single preparation, which involved patients with depressive disorders as defined by the standard criteria ICD-10 (International Statistical Classification of Diseases and Related Health Problems), DSM-IIIR (Diagnostical Manual) or DSM-IV and which used the Hamilton Depression (HAMD) Scale for measuring clinical outcomes. Six such trials involving 651 patients with mainly mild to moderately severe depressive disorders were included; two trials were placebo controlled and four compared St. John's wort with standard antidepressants. The studies lasted for 4–6 weeks and the doses of St. John's wort extract ranged from 200 to 900 mg daily; the range for total hypericin administered was 0.75–2.7 mg daily.

This meta-analysis showed that the response rate for St. John's wort was significantly greater than that for placebo (73.2 versus 37.9%, respectively, relative risk 1.48 and 95% CI 1.03–1.92) and similar to that observed with tricyclic antidepressants (64 versus 6.4% for St. John's wort and tricyclic antidepressants, respectively, relative risk 1.11 and 95% CI 0.92–1.29).[68] Despite the stringent inclusion criteria for trials in this meta-analysis, it was concluded that further studies are required in order to address methodological problems before it can be concluded that St. John's wort is an effective antidepressant.[68]

At least four randomised, controlled trials of monopreparations of St. John's wort involving patients with depressive disorders[64,69–71] have been published since the Cochrane review.[14] Two trials compared St. John's wort against placebo only,[64,69] one compared St. John's wort with fluoxetine[70] and one was a three-arm study comparing St. John's wort with imipramine and placebo.[71]

In a randomised, double-blind, multicentre study, 162 patients with mild to moderate depression received St. John's wort extract (ZE117) (250 mg) twice daily (equivalent to 1 mg hypericin daily) or placebo for six weeks.[69] At the end of the study, 56% of St. John's wort-treated patients compared with 15% of placebo recipients were classified as responders according to recognised criteria. The proportions of patients reporting adverse events were similar between groups (7.4 and 6.2% for St. John's wort and placebo, respectively).

Another randomised, double-blind, multicentre trial compared two different extracts of St. John's wort with placebo in 147 patients with mild or moderate depression according to DSM-IV criteria.[64] Patients received St. John's wort extract (300 mg, WS 5573, containing 0.5% hyperforin or 300 mg, WS 5572, containing 5% hyperforin) or placebo three times daily for six weeks. Patients who received the extract containing 5% hyperforin showed the largest reduction in Hamilton Rating Scale for Depression scores from baseline values. Furthermore, 49% of these patients were classified as treatment responders (according to recognised criteria), whereas 38.8 and 32.7% of patients who received 0.5% hyperforin and placebo recipients, respectively, were classified as responders. The proportions of patients reporting adverse events were similar (28.6 versus 28.6 versus 30.6% for 5% hyperforin, 0.5% hyperforin and placebo, respectively). These findings were the first to show that the therapeutic effect of St. John's wort in mild to moderate depression depends on its hyperforin content.[64]

In a study comparing St. John's wort with a selective serotonin reuptake inhibitor, 161 patients aged 60–80 years with mild or moderate depression according to ICD-10 criteria were randomised to receive St. John's wort extract (LoHyp-57) (400 mg) twice daily or fluoxetine (10 mg) twice daily for six weeks.[70] Neither the hypericin nor the hyperforin content of the St. John's wort extract were stated in a published report of the study. At the end of the treatment period, 71.4% of St. John's wort recipients and 72.2% of fluoxetine recipients were classified as responders according to recognised, pre-defined criteria. Similar efficacy for both St. John's wort and fluoxetine was demonstrated when data from subgroups of patients with mild and moderate depression were analysed. The numbers of patients developing adverse reactions with a possible or probable relationship to treatment were 12 and 17 for St. John's wort and fluoxetine, respectively, leading to cessation of treatment in six and eight cases, respectively.[70]

In a randomised, double-blind, multicentre trial in a primary care setting, 263 patients with moderate depression received St. John's wort extract (350 mg) three times daily (STEI 300, containing 0.2–0.3% hypericin and 2–3% hyperforin, $n = 106$), imipramine (100 mg) daily (in three divided doses of 50, 25 and 25 mg, titrated from 50 mg on day 1 and 75 mg on days 2–4, $n = 110$) or placebo ($n = 47$) for eight weeks.[71] Hypericum was found to be more effective than placebo after six weeks of treatment and to be as efficacious as imipramine after 8 weeks of treatment. In addition, both St. John's wort and imipramine were shown to improve quality of life, as measured by the SF-36, to a greater extent than placebo. Adverse events were reported by 22% of St. John's wort recipients, 46% of imipramine recipients and 19% of placebo recipients.

This study was criticised for its use of a relatively low dose of imipramine, such that the trial shows only that a comparatively high dose of St. John's wort seems to be as effective as a comparatively low dose of imipramine.[72] Nevertheless, this[71] and other new trials[64,69] have confirmed that St. John's wort extracts are more effective than placebo in mild to moderately severe depression.[72] However, further trials comparing St. John's wort with standard antidepressants, particularly newer classes of agents such as the selective serotonin reuptake inhibitors, are still required. A large placebo-controlled trial comparing St. John's wort extract (900–1800 mg daily) with the selective serotonin reuptake inhibitor sertraline (50–150 mg daily) in patients with major depression according to DSM-IV criteria is ongoing in the United States.[73] Published abstracts of randomised, double-blind, controlled trials have reported superiority of St. John's wort extract over placebo[74] and equivalent efficacy between St. John's wort and fluoxetine (20 mg) daily in mild to moderate depression[75,76] and between St. John's wort and imipramine (150 mg) daily.[76]

In a dose-ranging trial involving 348 patients with mild to moderate depression according to ICD-10 criteria, patients were randomised to receive St. John's wort extract three times daily equivalent to either 1 mg ($n = 119$), 0.33 mg ($n = 115$) or 0.17 mg ($n = 114$) hypericin for six weeks.[77] At the end of the treatment period, there was a significant reduction in HAMD scores compared with baseline values. The response rates (according to recognised criteria) were

68, 65 and 62% for 1, 0.33 and 0.17 mg hypericin, respectively; the differences between groups were not statistically significant. Thus, the study showed that there was no dose-dependent effect of hypericin in St. John's wort extracts.

Seasonal affective disorder The effects of St. John's wort extracts have been investigated in studies involving subjects with seasonal affective disorder (SAD),[78,79] although as yet there have not been any trials that have included a placebo control group. Twenty individuals with SAD were randomised to receive St. John's wort (LI 160) (300 mg) three times daily (equivalent to 0.9 mg hypericin) with or without bright light therapy.[78] After four weeks, there were significant reductions in HAMD scores in both groups compared with baseline values and there were no statistically significant differences between groups. Another study evaluated data from individuals with mild to moderate SAD who had used St. John's wort (300 mg) three times daily (equivalent to 0.9 mg hypericin) with ($n = 133$) or without light therapy ($n = 168$) for eight weeks.[79] The study was not randomised and involved data collection by postal questionnaires. Data from 301 returned questionnaires were suitable for analysis. Significant reductions in the mean SAD scores were observed in both groups compared with baseline values; the differences in the SAD scores between groups were statistically non-significant.

Antiviral activity Antiviral activity has been reported for hypericin against human immunodeficiency virus (HIV) and hepatitis C.[80,81,82,] Several uncontrolled studies in HIV-positive patients who received St. John's wort extract have reported immunologic and clinical benefits, including increases in CD4 cell counts in some patients.[83,84] In a phase I, dose-escalating study, 30 HIV-positive patients with CD4 cell counts < 350 cells/mm^3 received intravenous synthetic hypericin twice weekly (0.25 or 0.5 mg/kg body-weight), three times weekly (0.25 mg/kg) or oral hypericin daily (0.5 mg/kg).[85] Sixteen patients discontinued treatment early because of toxic effects, and phototoxicity in several other patients prevented completion of dose escalation. Antiretroviral activity as assessed by significant changes in HIV p24 antigen level, HIV titre, HIV RNA copies and CD4 cell counts was not observed.

Other studies The potential for the use of St. John's wort in 20 individuals presenting with fatigue[86] and in 19 women with self-reported premenstrual syndrome[87] has also been explored in uncontrolled pilot studies. Significant improvements in perceived fatigue and in symptoms of depression and anxiety were seen after six weeks' treatment with St. John's wort (equivalent to 0.9 mg hypericin daily) compared with baseline values[86] and in overall premenstrual syndrome scores after treatment with St. John's wort (equivalent to 0.9 mg hypericin daily) for two menstrual cycles.[87] Thus, there is scope for conducting randomised controlled trials of St. John's wort in these conditions.[86,87]

In a randomised, double-blind, placebo-controlled trial, 179 women with menopause-related psychovegetative symptoms received a combination preparation of St. John's wort and black cohosh (*Cimicifuga racemosa*) or placebo for six weeks.[88] The results indicated that the combination product had a significantly greater effect on the symptoms than did placebo. Postmarketing surveillance studies have been carried out with extracts of St. John's wort in patients with psychovegetative disorders[89] and in women with menopausal symptoms of psychological origin[90] (*see* Side-effects, Toxicity). Improvements in symptom scores compared with baseline values following treatment with St. John's wort extracts were reported in all studies; these studies did not involve a control group.

A randomised, double-blind, phase I study involving 55 healthy volunteers who received St. John's wort (900 mg) daily (containing 0.5% hyperforin), St. John's wort (900 mg) daily (containing 5.0% hyperforin) or placebo for eight days investigated the effects on quantitative electroencephalogram as an indicator of drug-induced pharmacological action.[91] Reproducible central pharmacodynamic effects were apparent in both groups of St. John's wort recipients compared with placebo recipients. The effects were greater in subjects who received extract containing 5.0% hyperforin than in those who received extract containing 0.5% hyperforin.

Placebo-controlled, crossover studies investigating the effects of St. John's wort (0.9 and 1.8 mg) on the sleep polysomnogram of healthy subjects reported that both doses of St. John's wort significantly increased rapid eye movement (REM) sleep latency compared with placebo, but had no effect on REM sleep duration or other parameters of sleep architecture.[92]

In a randomised, double-blind, placebo-controlled trial involving 23 overweight but otherwise healthy adults, subjects who received treatment with St. John's wort (900 mg) daily, *Citrus aurantium* extract (975 mg) daily and caffeine (528 mg) daily lost significantly more body weight than did subjects in the placebo and no-treatment control groups.[93]

A placebo-controlled, crossover study in 19 healthy volunteers who received St. John's wort for

15 days either alone or in combination with ethanol (to achieve a blood alcohol concentration of 0.05%) reported that there were no differences between the two groups in sense of well-being or adverse events.[94]

A randomised, double-blind, placebo-controlled, six-week trial involving 72 long-distance runners and triathletes reported significant improvements in endurance capacity in subjects who received vitamin E with St. John's wort compared with subjects who received vitamin E alone or placebo.[95]

Pharmacokinetics Detailed pharmacokinetic studies have been carried out with the hypericin-standardised St. John's wort extract LI 160.[96] Administration of single oral doses of LI 160 (300, 900 and 1800 mg) to healthy male volunteers resulted in peak plasma hypericin concentrations of 1.5, 7.5 and 14.2 ng/mL for the three doses, respectively. Peak plasma concentrations were seen with hypericin after 2.0–2.6 hours and with pseudohypericin after 0.4–0.6 hours. The elimination half-life of hypericin was between 24.8 and 26.5 hours. Repeated doses of LI 160 (300 mg) three times daily resulted in steady-state concentrations after four days.[96] Oral administration of the St. John's wort extract WS 5572 (300 mg, equivalent to 14.8 mg hyperforin) resulted in peak plasma concentrations of 150 ng/mL being reached 3.5 hours after administration.[97] The elimination half-life was 9 hours. Following repeated doses of 300 mg three times daily, the estimated steady-state plasma hyperforin concentrations were 100 ng/mL. Other studies investigating the pharmacokinetics of hypericum and hypericin have been summarised.[1,G1]

Side-effects, Toxicity

A review of safety data for St. John's wort obtained from reports of randomised controlled trials, drug monitoring and postmarketing surveillance studies[98–101] and national and international drug safety monitoring bodies has been published.[102] Collectively, the data indicate that St. John's wort is well-tolerated. Adverse effects are generally mild; the most common adverse effects reported are gastrointestinal symptoms, dizziness, confusion and tiredness/sedation. In placebo-controlled trials, the frequency of adverse effects with St. John's wort is similar to that for placebo.[102] Photosensitivity appears to be an extremely rare event with recommended doses of St. John's wort (*see below*).[102]

Several postmarketing surveillance studies of the St. John's wort extracts HYP811,[89,103] LI 160[90,104] and Neuroplant[105] have since been published. These studies provide further confirmation of the tolerability of St. John's wort extracts taken at recommended doses for short-term treatment (usually 4–6 weeks, although one study monitored 111 women for 12 weeks[90]). The frequency of adverse reactions in 6382 patients with mild depression who took St. John's wort for six weeks was reported to be 0.125% (mainly skin reactions).[105]

A systematic review and meta-analysis of randomised controlled trials of St. John's wort in patients with mild to moderately severe depressive disorders reported that, in the trials comparing St. John's wort with standard antidepressants, the proportions of patients reporting side-effects were 26.3 and 44.7%, respectively (rate ratio 0.57 and 95% CI 0.4–0.69).[14] However, further studies investigating the long-term safety of St. John's wort were advised. Another meta-analysis which employed tighter inclusion criteria reported that tricyclic antidepressants were associated with a higher proportion of side-effects than were St. John's wort preparations (47 versus 26.4%, respectively, relative risk 1.72 and 95% CI 1.30–2.14).[68] Randomised controlled trials[64,69–71] published since the Cochrane meta-analysis[14] and published abstracts[74–76] have also reported that St. John's wort has a more favourable short-term safety profile than standard antidepressants[70,71,75,76] and that the frequency of adverse events seen with St. John's wort is similar to that for placebo[64,69,71,74] (*see* Clinical studies). In a comparative trial of St. John's wort and fluoxetine, the frequency of adverse reactions associated with St. John's wort was higher than expected, although it was stated that the effects reported were similar to those known to occur with fluoxetine.[70] The observation that the frequency of adverse effects is lower in placebo-controlled trials of St. John's wort than in comparative trials with standard antidepressants has been made previously.[102] A review has attempted to compare the safety profile of St. John's wort systematically with that of several conventional antidepressants.[106]

Photosensitivity Sensitivity to sunlight following the ingestion of hypericum or hypericin is known as hypericism.

Delayed hypersensitivity or photodermatitis has been documented for St. John's wort following the ingestion of a herbal tea made from the leaves.[107] Hypericin is stated to be the photosensitising agent present in St. John's wort.[82,G33,G47] A review of the photodynamic actions of hypericin has been published.[108] In a double-blind, crossover, single-dose study in 13 healthy volunteers who received placebo or St. John's wort extract (LI 160) (900, 1800 and 3600 mg containing 0, 2.81, 5.62 and 11.25 mg total hypericin, respectively), no evidence of photosensitivity was observed with or without St. John's wort

following skin irradiation with both UV-A and UV-B light 4 hours after dosing.[109] In a multiple-dose study in which 50 volunteers received St. John's wort (LI 160) (600 mg) three times daily (equivalent to 5.6 mg total hypericin daily) for 15 days, a moderate increase in UV-A sensitivity was observed.[109] However, the doses used were higher than those recommended therapeutically. In another single-dose study, administration of St. John's wort (LI 160) (1800 mg, equivalent to 5.4 mg total hypericin) to 12 healthy volunteers resulted in a mean serum total hypericin concentration of 43 ng/mL and a mean skin blister fluid concentration of 5.3 ng/mL.[110] After administration of St. John's wort (300 mg) three times daily for seven days in order to achieve steady-state concentrations, the mean serum total hypericin concentration was 12.5 ng/mL and the mean skin blister fluid concentration was 2.8 ng/mL; these concentrations are below those estimated to be phototoxic (>100 ng/mL).[110]

The consumption of large quantities of St. John's wort by grazing animals has been associated with the development of photosensitivity.[111,G22,G51] Mice given 0.2–0.5 mg of the herb were found to develop severe photodynamic effects.[G22] Studies using cell cultures of human keratinocytes incubated with hypericin or St. John's wort extract and exposed to UV-A resulted in a reduction in the LC_{50} (lethal concentration) with hypericin, but only a mild reduction with hypericum.[112] From these findings it has been estimated that at least 30 times the therapeutic dose would be necessary to produce phototoxic effects in humans.[112] Experimental evidence has suggested that a solution of hypericin can react with visible and UV light to produce free radical species and that this may lead to damage of proteins in the lens of the eye.[113] There are no reports of cataract formation in individuals who have taken St. John's wort.

A study reported that HIV-positive patients treated with oral hypericin (0.05 mg/kg) for 28 days developed mild symptoms of photosensitivity on exposure to sunlight and that two patients developed intolerable symptoms of photosensitivity when the dose was increased to 0.16 mg/kg.[114] In a dose-escalating study involving 30 HIV-infected patients treated with oral (0.5 mg/kg daily) or intravenous hypericin (starting dosage 0.25 mg/kg twice or three times weekly), 16 patients discontinued treatment before completing eight weeks of therapy because of moderate or severe phototoxicity; severe cutaneous phototoxicity was observed in 11 out of 23 evaluable patients.[85] Other serious clinical or laboratory adverse events were infrequent: elevation of alkaline phosphatase and hepatic aminotransferase concentrations to more than five times normal values was noted in two and three patients, respectively.

Other effects *In humans* A case of subacute toxic neuropathy possibly related to the use of St. John's wort and subsequent exposure to sunlight has been reported.[115] A woman developed stinging pains in areas exposed to the sun (face and hands) four weeks after starting treatment with St. John's wort (500 mg/day, extract and hypericin content not stated); the report did not state whether the woman was using any other products. Her symptoms improved three weeks after stopping St. John's wort and disappeared over the next two months.

There have been reports of sensory nerve hypersensitivity occurring in individuals who have taken St. John's wort preparations (tablets or tinctures).[116]

Cases of mania[117,118] and hypomania[119,120] have been reported in individuals taking St. John's wort preparations. Two cases of mania were reported in patients with bipolar depression who began self-treatment with standardised St. John's wort extract (900 mg) daily[118] and one in a patient experiencing a moderate depressive episode who was taking both sertraline and St. John's wort (dosage not known).[117] A case of hypomania was reported in a woman with panic disorder and unipolar major depression who had discontinued sertraline treatment one week before starting St. John's wort tincture.[119] Two cases of hypomania were reported in individuals with no history of bipolar disorder.[120] A man who had received electroconvulsive therapy and who had previously taken various antidepressant drugs, including venlafaxine, fluvoxamine, moclobemide and nortriptyline, experienced a hypomanic episode six weeks after starting St. John's wort (dosage not stated). A man with symptoms of post-traumatic stress disorder was diagnosed with an acute manic episode after three months of self-treatment with St. John's wort (dosage not stated).[120]

Several of these reports stated that the symptoms had resolved after stopping treatment with St. John's wort, although in one case the patient improved but remained agitated despite cessation of St. John's wort.[120] None of the cases involved rechallenge with St. John's wort and, in all cases, there were other pharmacological factors and/or underlying illnesses that could have been responsible for or contributed to the precipitation of mania.

In animals and in vitro studies Experimental studies investigating the genotoxic potential and mutagenic activity of St. John's wort extracts *in vitro* and *in vivo* have been summarised.[G1,G52] *In vivo* studies and most *in vitro* studies provided negative results, indicating a lack of mutagenic potential with defined St. John's wort extracts.[G52] Mutagenic activity observed in an *in vitro* Ames test was attributed to

the presence of quercetin, although other studies have found no mutagenic potential with a St. John's wort extract and it has been stated that there is no valid evidence for the carcinogenicity of quercetin in humans.[G1,G52]

Dietary administration of St. John's wort to rats was found to have no affect on various hepatic drug-metabolising enzymes (e.g. aminopyrine, *N*-demethylase, glutathione *S*-transferase and epoxide hydrolase) or on copper concentrations in the liver (*see* Contra-indications, Warnings, Drug interactions). No major effects were observed on hepatic iron or zinc concentrations and no significant tissue lesions were found in four rats fed St. John's wort in their daily diet for 119 days (10% for first 12 days and 5% thereafter because of unpalatability).[121]

Cytotoxic constituents related to hyperforin have been isolated from two related *Hypericum* species (*see In vitro* and animal studies).

Contra-indications, Warnings

Individuals with sensitivity towards St. John's wort may experience allergic reactions. The use of St. John's wort is not advised in known cases of photosensitivity and, in view of the potential of hypericin as a photosensitising agent, therapeutic UV treatment should be avoided whilst using St. John's wort.[G1]

It has previously been suggested that excessive doses of St. John's wort may potentiate monoamine oxidase inhibitor therapy.[122] However, as monoamine oxidase inhibitory activity has not been reported *in vivo* with St. John's wort, this warning is no longer considered necessary. In addition, avoidance of foodstuffs, such as those containing tyramine (e.g. cheese, wine, meat and yeast extracts) and medicines containing sympathomimetic agents (e.g. cough/cold remedies), which interact with MAOIs, is not considered necessary.

Drug interactions Recent evidence has emerged from spontaneous reports[123] and published case reports[124–127] of interactions between St. John's wort and certain prescribed medicines, leading to a loss of or reduction in the therapeutic effect of these prescribed medicines. Drugs that may be affected include indinavir, warfarin, cyclosporin, digoxin, theophylline and oral contraceptives. Drug interaction studies in healthy volunteers have provided supporting evidence of interactions between St. John's wort and phenprocoumon[128] and digoxin[129] and have provided evidence that St. John's wort may induce some cytochrome P450 (CYP) drug-metabolising enzymes in the liver,[128,130,131] namely CYP3A4, CYP1A2 and CYP2CP, as well as affecting P-glycoprotein (a transport protein). Other studies have failed to find significant effects on CYP isoenzymes,[132–134] although the numbers of volunteers may have been too small and the duration of St. John's wort administration too short to exclude an inductive effect truly.[133,134]

There have been other reports of increased serotonergic effects in patients taking St. John's wort concurrently with selective serotonin reuptake inhibitors (e.g. sertraline, paroxetine).[135,136]

Also of concern is that the content of active constituents can vary between different preparations of St. John's wort; thus, the degree of enzyme induction may vary.

Collectively, these data led the UK Committee on Safety of Medicines (CSM) to issue advice to pharmacists, doctors and patients on the use of St. John's wort with certain drugs.[137,138] The CSM's advice for healthcare professionals for patients taking St. John's wort and certain drugs can be summarised as follows.

Warfarin, cyclosporin, digoxin, theophylline and anticonvulsants (carbamazepine, phenobarbitone and phenytoin) There is a risk of reduced therapeutic effect, e.g. risk of transplant rejection, seizures and loss of asthma control. Advice is to check plasma drug concentrations (with warfarin, the patient's International Normalised Ratio should be checked) and to stop St. John's wort therapy. In addition, dose adjustment may be necessary.

HIV protease inhibitors (indinavir, nelfinavir, ritonavir and saquinavir) and HIV non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) There is a risk of reduced blood concentrations with possible loss of HIV suppression. Advice is to measure HIV RNA viral load and to stop St. John's wort.

Oral contraceptives There is a risk of reduced blood concentrations, breakthrough bleeding and unintended pregnancy. Advice is to stop St. John's wort.

Triptans (sumatriptan, naratriptan, rizatriptan and zolmitriptan) and selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) There is a risk of increased serotonergic effects with the possibility of an increased risk of adverse reactions. Advice is to stop St. John's wort.

Patients already taking any of the above drugs should be advised not to start taking St. John's wort and users of other medicines should be advised to seek professional advice before using St. John's wort. Topical medicines and non-psychotropic medicines

that are excreted renally are not likely to interact with St. John's wort. In addition, topical or homeopathic preparations of St. John's wort are not likely to interact with prescribed medicines.

Pregnancy and lactation Slight *in vitro* uterotonic activity has been reported for St. John's wort (*see In vitro* and animal studies).

There is a report of a 38-year-old woman who started taking St. John's wort (900 mg/day) at her 24th week of pregnancy, taking the last dose 24 hours before delivery.[139] The pregnancy was unremarkable except for late onset of thrombocytopenia. Another report described a 43-year-old woman who discontinued fluoxetine and methylphenidate upon becoming pregnant and started taking St. John's wort (900 mg/day). The report does not state the outcome of the pregnancy,[139] although it is assumed that had adverse events occurred, they would have been stated. In view of the lack of toxicity data, St. John's wort should not be used during pregnancy and lactation.

Pharmaceutical Comment

The chemical composition of St. John's wort has been well studied. Documented pharmacological activities provide supporting evidence for several of the traditional uses stated for St. John's wort. Many pharmacological activities appear to be attributable to hypericin and to the flavonoid constituents; hypericin is also reported to be responsible for the photosensitive reactions that have been documented for St. John's wort. With regard to the antidepressant effects of St. John's wort, hyperforin rather than hypericin, as originally thought, has emerged as one of the major constituents responsible for antidepressant activity. However, further research is required in order to determine which other constituents contribute to the antidepressant effect.

Evidence from randomised, controlled trials has confirmed the efficacy of St. John's wort extracts over placebo in the treatment of mild to moderately severe depression.[14] Other randomised controlled studies have provided some evidence that St. John's wort extracts are as effective as some standard antidepressants in mild to moderate depression. However, there is still a need for further trials in order to assess the efficacy of St. John's wort extracts compared with that of standard antidepressants, particularly newer antidepressant agents such as the selective serotonin reuptake inhibitors. In addition, there is generally a need for further studies in well-defined groups of patients, in different types of depression and conducted over longer periods in order to determine long-term safety.[14] St. John's wort does appear to have a more favourable short-term safety profile than standard antidepressants, a factor that is likely to be important in patients continuing to take medication. Concerns have been raised over interactions between St. John's wort and certain prescribed medicines (including warfarin, cyclosporin, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, triptans and oral contraceptives); advice is that patients taking these medicines should stop taking St. John's wort, generally after seeking professional advice as dose adjustment may be necessary. With the exception of oral contraceptives, patients taking these prescribed medicines should not be self-treating with over-the-counter medicines, including herbal medicines, without first seeking professional advice.

In view of the lack of long-term safety data for St. John's wort and its reported photosensitising ability, excessive use of St. John's wort should be avoided.

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See also General References G1, G2, G3, G5, G7, G9, G15, G16, G18, G22, G28, G31, G32, G33, G36, G37, G40, G43, G45, G46, G48, G50, G51, G52, G56, G61, G62 and G64.

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