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Review

St John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties

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Abstract

The chemical composition of St. John's wort has been well-studied. Documented pharmacological activities, including antidepressant, antiviral, and antibacterial effects, 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. Further research is required 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. 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. There is still a need for further trials 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 (recent comparative studies with fluoxetine and sertraline have been conducted). Also, there is 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. St John's wort does appear to have a more favourable short-term safety profile than do 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, ciclosporin, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, triptans, oral contraceptives); advice is that patients taking these medicines should stop taking St John's wort, generally after seeking professional advice as dose adjustment of conventional treatment may be necessary.

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Introduction

St John's wort (also known as hypericum, millepertuis) is *Hypericum perforatum* L., Hypericaceae, a herbaceous perennial plant native to Europe and Asia, and which has been introduced into the United States where it has naturalised (Bombardelli & Morazzoni 1995; *American Herbal Pharmacopeia* 1997). There are several explanations as to the origins of the names hypericum and St John's wort. Commonly, the name hypericum is believed to be derived from the Greek words

hyper (over) and *eikon* (image), and the name St John's wort may have arisen as the flowers bloom around St John's Day (June 24).

St. John's wort is stated to possess sedative and astringent properties, and has been used traditionally for the treatment of excitability, neuralgia, fibrositis, sciatica, menopausal neurosis, anxiety, depression and as a nerve tonic, and in topical preparations for the treatment of wounds (Newall et al 1996). St. John's wort is used extensively in herbal products as well as in homoeopathic preparations. The plant is also used in foods. It is classified by the Council of Europe as a natural source of food flavouring (category 5), with limits on hypericin and xanthones (Council of Europe 2000).

Today, St John's wort is best known for its use in the treatment of mild-to-moderately severe depressive disorders. It is one of the top-selling herbal products – sales figures for 1997 were reported to have been almost US $48 million (Isenberg 1998); another analysis found that sales of St John's wort increased by 2800 % in one year (Brevoort 1998).

Several pharmacopoeial and other monographs on St John's wort have been produced (*British Herbal Pharmacopoeia* 1996; *European Scientific co-operative on phytotherapy* (*ESCOP*) 1996; *American Herbal Pharmacopeia* 1997; Parfitt 1999; Barnes et al 2000; *European Pharmacopoeia* 2000).

Chemistry

The major active constituents are considered to be hyperforin (a prenylated phloroglucinol; Figure 1) and hypericin (a naphthodianthrone; Figure 2), although other biologically active constituents, eg flavonoids, tannins, are also present (Nahrstedt & Butterweck 1997). The constituents of St John's wort (*Hypericum perforatum* L.), compiled from several sources (Bisset 1994; Bombardelli & Morazzoni 1995; Newall et al 1996; *American Herbal Pharmacopeia* 1997), are presented below.

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. Hypericin content (around 0.1 to 0.15 %) is taken to include both hypericin and pseudohypericin (Vanhaelen & Vanhaelen-Fastre 1983) 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) (Berghöfer & Hölzl 1987, 1989), catechins (flavonoids often associated with condensed tannins) (Ollivier et al 1985; Hoelzl & Ostrowski 1987). Concentrations of rutin, hyperoside, and isoquercitrin have been reported as 1.6 %, 0.9 %, and 0.3 %, respectively (Dorossiev 1985).

Prenylated phloroglucinols
Hyperforin (2.0 to 4.5 %), adhyperforin (0.2 to 1.9 %) (Brondz et al 1982; Ollivier et al 1985; Ayuga & Rebuelta 1986; *American Herbal Pharmacopeia* 1997), oxygenated analogues of hyperforin (Trifunovic et al 1998; Verotta et al 1999, 2000).

Tannins (8–9 %)
Type not specified. Proanthocyanidins (condensed type) have been reported (Bisset 1994).

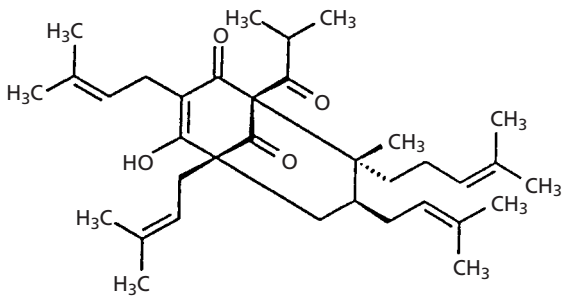

Figure 1 Chemical structure of hyperforin

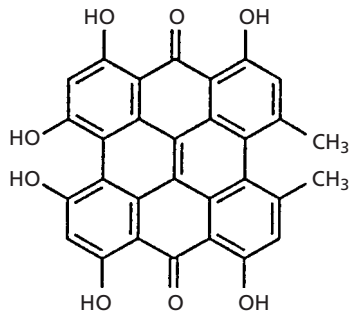

Figure 2 Chemical structure of hypericin

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; Brondz et al 1983), α- and β-pinene, α- terpineol, geraniol, and traces of myrcene and limonene (monoterpenes), caryophyllene and humulene (sesquiterpenes) (Mathis & Ourisson 1964a, b)

Other constituents
Acids (isovalerianic, nicotinic, myristic, palmitic, stearic), carotenoids, choline, nicotinamide, pectin, β-sitosterol, straight chain saturated hydrocarbons (C16, C30) and alcohols (C24, C26, C28) (Mathis & Ourisson 1964c; Brondz et al 1983).

Pharmacology

Several pharmacological activities, including antidepressant, antiviral, and antibacterial effects, have been documented for extracts of St John's wort and/or its constituents (Bombardelli & Morazzoni 1995; *American Herbal Pharmacopeia* 1997; Chatterjee 1998a; Schulz et al 1998; Nathan 1999; Mills & Bone 2000).

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. However, experimental (Chatterjee et al 1998a, b) and clinical evidence (Laakmann et al 1998) has now emerged to indicate that hyperforin is one of the major constituents required for antidepressant activity.

In-vitro and animal studies. Inhibition of monoamine oxidase (MAO) type A and B in rat brain mitochondria in-vitro was described for hypericin (Suzuki et al 1984). However, other studies have reported only weak or no MAO inhibition (Demisch et al 1989; Bladt & Wagner 1994; Thiede & Walper 1994; Yu 2000). 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 $GABA_B$, concentrations of hypericum required were unlikely to be attained after oral administration in humans (Cott 1997). Other biochemical studies reported that the hypericum extract LI 160 was only a weak inhibitor of MAO-A and MAO-B activity, but that it inhibited the synaptosomal uptake of serotonin (5-hydroxytryptamine; 5-HT), dopamine and norepinephrine (noradrenaline) with approximately equal affinity and also led to a down-regulation of beta-receptors and an upregulation of $5\text{-}HT_2$ receptors in rat frontal cortex (Müller et al 1997). However, in-vitro incubation of mononuclear cells from normal human donors with *H. perforatum* extract (LI 160S) failed to enhance natural killer cell activity (NKCA) (Helgason et al 2000). By contrast established stimulators of NKCA, for example the selective serotonin reuptake inhibitor paroxetine, augmented NKCA above that seen with control (Helgason et al 2000). Since serotonergic activity is associated with increases in NKCA, *H. perforatum* may possess only weak serotonergic activity (Helgason et al 2000).

The effects of fluoxetine and hypericin- and flavonoid-standardised hypericum extracts (LI 160: 0.3% hypericin, 6% flavonoids; Ph-50: 0.3% hypericin, 50% flavonoids) on concentrations of neurotransmitters in brain regions were studied in rats (Calapai et al 1999). All three preparations induced a significant increase in 5-HT concentrations in rat cortex, both LI 160 and Ph-50 caused increases of norepinephrine and dopamine in rat diencephalon, and Ph-50 also induced an increase in norepinephrine content in the brainstem, areas that are implicated in depression (Calapai et al 1999).

Hyperforin has been shown to be an uptake inhibitor of 5-HT, dopamine, norepinephrine, GABA and L-glutamate in synaptosomal preparations (Chatterjee et al 1998a; Wonnemann et al 2000), and to inhibit 5-HT uptake in rat peritoneal cells in a dose-dependent manner (Chatterjee et al 1998b). Studies have also described discrepancies between observed and theoretical IC50 values, indicating that hyperforin is not the only component of hypericum extract that is responsible for the observed effects (Chatterjee et al 1998b; Gobbi et al 1999). 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 (Singer et al 1999) and that this may be secondary to activation of the Na^+/H^+ exchange as a result of a decrease in intracellular pH (Singer et al 2000). 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 limit-

ing factor for 5-HT uptake inhibition in-vivo (Uebelhack & Franke 2000).

In studies utilising the rat forced swimming test, an experimental model of depression, hypericum extracts induced a significant reduction in immobility (De Vry et al 1999; Panocka et al 2000). One of these studies, which involved a dry extract of hypericum containing 0.3% hypericin and 3.8% hyperforin, reported that the antidepressant activity may be mediated by interaction with sigma receptors and by increased serotonergic transmission (Panocka et al 2000). Pure hyperforin and hypericum extract also demonstrated antidepressant activity in a behaviour despair test in rats (Chatterjee et al 1998b).

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 (Gambarana et al 1999). Flavonoid fractions, and flavonoids isolated from these fractions, have been reported to have antidepressant activity in experimental studies (forced swimming test) in rats (Butterweck et al 2000).

Clinical studies. A double-blind, placebo-controlled, cross-over 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 hypericin 0.3%) on plasma concentrations of growth hormone, prolactin and cortisol (Franklin et al 1999). A significant increase in plasma growth hormone concentration, and a significant decrease in plasma prolactin concentration was 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, to assess dose–response relationships, and to determine whether there is evidence for effects on dopaminergic systems in patients with depression treated with St John's wort (Franklin et al 1999). Another study, which utilised a randomised, 3-way, cross-over design, investigated the effects of a single dose of St John's wort extract (LI 160S) 600 mg, 300 mg, or placebo, on hormone concentrations in 12 healthy male volunteers (Laakman et al 2000). Compared with placebo, St John's wort extract (600 mg) increased cortisol secretion between 30 and 90 min after dosing, indicating an influence of St John's wort on certain CNS neurotransmitters. There was no difference between the 3 groups with regard to adrenocorticotrophic hormone, growth hormone and prolactin secretion.

Antimicrobial activity

Hyperforin is reported to have antibacterial activity against *Staphylococcus aureus* (Brondz et al 1982). Antibacterial activity of hyperforin against multidrug-resistant *S. aureus* and Gram-positive bacteria, including *Streptococcus pyogenes* and *Corynebacterium diphtheriae*, has been reported (Schempp et al 1999b). However, it has been emphasised that the antibacterial effects of hyperforin are only observed at high concentrations (Fiebich et al 1999; Voss & Verweij 1999). 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* (Schempp et al 1999b).

Antiviral activity

Flavonoid- and catechin-containing fractions of St John's wort have exhibited activity against influenza virus (Mishenkova et al 1975). Hypericin and pseudohypericin have been reported to inhibit several encapsulated viruses in-vitro, including herpes simplex virus types 1 and 2 (Wood et al 1990; Weber et al 1994), and human immunodeficiency virus (HIV)-1 (Meruelo et al 1988; Lavie et al 1989; Hudson et al 1991; Lopez-Bazzocchi et al 1991). Hypericin has also been reported to inactivate murine cytomegalovirus (MCMV) and Sindbis virus (Hudson et al 1991). The antiviral activity of hypericin appears to involve a photoactivation process (Hudson et al 1991; *American Herbal Pharmacopeia* 1997).

Other activities

Several other pharmacological actions have been documented for hypericum, some of which may be related to its antidepressant effect.

In-vitro studies using a hamster vas deferens smooth muscle cell line demonstrated that hyperforin induces release of calcium ions from mitochondrial or other sources, followed by an activation of cellular metabolism (Koch & Chatterjee 2000). It is not known if this activity contributes to the antidepressant effects of hyperforin.

Depression and alcoholism are thought to have some neurochemical similarities, such as low brain serotonin concentrations (Ballenger et al 1979). Oral administration of a single dose of St John's wort (100, 200, 400, 600 or 800 mg kg^{-1}) to two strains of alcohol-preferring rats significantly reduced alcohol intake in both strains (Rezvani et al 1999). In another study in experimental alcoholism, acute intraperitoneal administration of St John's wort 10 to 40 mg kg^{-1}, fluoxetine 1–10 mg kg^{-1} and imipramine 3–30 mg kg^{-1} reduced alcohol intake in a dose-dependent manner in a 12-h

limited access two-bottle choice (ethanol/water) procedure (De Vry et al 1999). Dry hypericum extract containing 0.3% hypericin and 3.8% hyperforin was found to inhibit 10% ethanol intake in alcohol-preferring rats; however, the inhibitory effect was not modified by pre-treatment with either intraperitoneal rimcazole (a sigma receptor antagonist) or intracerebroventricular 5,7-dihydroxytryptamine, suggesting that interaction with sigma receptors and effects on serotonergic systems may be unimportant in hypericum's effect on ethanol intake (Panocka et al 2000).

A study in rats explored the potential anxiolytic activity of *H. perforatum* total extract, a fraction containing hypericin and pseudohypericin, and pure protohypericin (Vandenbogaerde et al 2000). *H. perforatum* total extract was found to increase locomotor activity in an open-field test, and to have an anxiolytic-like effect in a light–dark test, whereas the single components did not show any such effects. Furthermore, the anxiolytic activity was blocked by pre-treatment with the benzodiazepine receptor antagonist flumazenil (Vandenbogaerde et al 2000).

Oral administration of a standardised 50% ethanolic extract of Indian *H. perforatum* 100 and 200 mg kg^{-1} once daily for three days in rat models of learning and memory resulted in significant attenuation of scopolamine- and sodium-nitrite-induced impaired retention of active avoidance. This was comparable to that seen with intraperitoneal piracetam 500 mg kg^{-1} (a nootropic agent) (Kumar et al 2000).

An extract of St. John's wort was found to suppress inflammation and leucocyte infiltration in mice, induced by carrageenan and PGE_1 (Shipochliev et al 1981). In-vitro, hypericin has been shown to inhibit tumour-necrosis-factor–induced activation of the transcription factor NF-κB (Bork et al 1999), to inhibit specific growth-factor-regulated protein kinases (Takahashi et al 1989; De Witte et al 1993; Agostinis et al 1995), and to inhibit the release of arachidonic acid and leukotriene B_4 (Panossian et al 1996). In a rabbit model of proliferative vitreoretinopathy (PVR), intravitreal injection of hypericin 0.1 mL (10 or 100 μM, but not 1 μM) inhibited the progression of PVR when compared with severity in control eyes 5 days after hypericin administration (Tahara et al 1999). 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 (Bezáková et al 1999). Other compounds may contribute to the anti-inflammatory properties of St John's wort (Fiebich et al 1999). Anti-inflammatory and anti-ulcerogenic properties have been documented for amentoflavone, a biapigenin derivative (Berghöfer & Hölzl 1987). Incubation of human epidermal cells with hyperforin was found to suppress the proliferation of alloreactive T cells, compared with control, and also to inhibit the proliferation of peripheral blood mononuclear cells in a dose-dependent manner (Schempp et al 2000a). A study investigating the absorption of hypericin into the skin of hairless mice demonstrated that emulsifying ointment with polyethylene glycol was an effective delivery vehicle for hypericin (Kamuhabwa et al 2000a).

The photoactivating effect of hypericin has been investigated in-vitro in several cancer cell lines, and in-vivo in animal models of cancer. Incubation of prostatic adenocarcinoma cells and a metastatic cell line of human prostate cancer with hypericin 0.001 to 0.3 μg mL^{-1} followed by laser irradiation resulted in phototoxic effects on both cell lines, whereas no effect was seen in the absence of irradiation (Colasanti et al 2000). Similar studies in-vitro have demonstrated photocytotoxicity in human urinary bladder carcinoma cells (Kamuhabwa et al 2000b) and in pancreatic cancer cell lines incubated with hypericin and then exposed to green laser light (Liu et al 2000). In-vivo studies in nude mice in which pancreatic cancer cells had been implanted in the pancreas, followed by intratumoural administration of hypericin and laser phototherapy resulted in decreased pancreatic cancer cell growth, compared with that in paired controls (Liu et al 2000). Also, laser intratumoural photodynamic therapy with hypericin to tumours grown in mice following transplantation of human squamous carcinoma cells resulted in a significant induction in tumour necrosis, compared with laser treatment alone (Chung et al 2000).

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 (Melzer et al 1988).

Tannins isolated from St. John's wort are stated to have mild astringent activity (Grujic-Vasic et al 1986).

Clinical pharmacokinetics

Detailed pharmacokinetic studies have been carried out with the hypericin-standardised St John's wort extract LI 160 (Biber et al 1998). Administration of single oral doses of LI 160 300, 900, or 1800 mg to healthy male volunteers resulted in peak plasma hypericin concen-

trations of 1.5, 7.5 and 14.2 ng mL^{-1} for the three doses, respectively. Peak plasma concentrations were seen with hypericin after 2.0 to 2.6 h and with pseudohypericin after 0.4 to 0.6 h. The elimination half-life of hypericin was between 24.8 and 26.5 h. Repeated doses of LI 160 300 mg three times daily resulted in steady state concentrations after four days (Biber et al 1998). Oral administration of the St John's wort extract WS 5572 300 mg (equivalent to 14.8 mg hyperforin) resulted in peak hyperforin plasma concentrations of 150 ng mL^{-1} reached 3.5 h after administration (Staffeldt et al 1994). The elimination half-life was 9 h. Following repeated doses of 300 mg three times daily, estimated steady state plasma hyperforin concentrations were 100 ng mL^{-1}. Other studies investigating the pharmacokinetics of hypericum and hypericin have been summarised (Bombardelli & Morazzoni 1995; *American Herbal Pharmacopeia* 1997).

Therapeutic activity

Clinical trials with extracts of St John's wort have focussed 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

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 (Linde et al 1996). 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 (Linde & Mulrow 2001). 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, one study involved a combination product of St John's wort extract with 4 other herbal ingredients); the ten other trials (involving 1123 patients) compared St John's wort extract with conventional antidepressant or sedative drugs, including amitriptyline, imipramine, desipramine and maprotiline (8 trials used single-ingredient preparations, 2 used combinations of St John's wort and valerian). St John's wort extract was administered at doses ranging from 350 to 1800 mg; the hyperforin content of preparations tested was not known. Most trials lasted for 4 to 6 weeks, although some studies were conducted for 3 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; 95% confidence intervals (CI): 1.69 to 3.61). St John's wort preparations were found to be as effective as conventional antidepressant agents (single preparations, rate ratio: 1.01; 95% CI: 0.87 to 1.16), although for several reasons – for example, the use of low doses of conventional antidepressants, trials involved small numbers of patients – this evidence was considered inadequate to establish whether St John's wort was as effective as conventional antidepressant drugs (Linde & Mulrow 2001). Further studies comparing St John's wort preparations with standard antidepressant agents in well-defined patient groups and over longer periods were considered necessary (Linde & Mulrow 2001). The proportions of patients involved in the studies reporting side effects for hypericum preparations and conventional antidepressants were 26.3% and 44.7%, respectively (rate ratio: 0.57; 95% CI: 0.47 to 0.69).

Another meta-analysis used tighter inclusion criteria for trials in an attempt to increase the validity of the analysis (Kim et al 1999). It included only randomised, blinded, controlled trials of St John's wort (as a single preparation), involving patients with depressive disorders as defined by the standard criteria ICD-10 (International Statistical Classification of Diseases and Related Health Problems), DSM-IIIR (Diagnostic and Statistical Manual) or DSM-IV and which utilised the Hamilton Depression (HAMD) Scale to measure 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. Studies lasted for 4 to 6 weeks, and doses of St John's wort extract ranged from 200 to 900 mg daily; the range for total hypericin administered was 0.75 to 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% *vs* 37.9%, respectively; relative risk: 1.48; 95% CI: 1.03 to 1.92) and similar to that observed with tricyclic antidepressants (64% *vs* 66.4% for St John's wort and tricyclic antidepressants, respectively; relative risk: 1.11; 95% CI: 0.92 to 1.29) (Kim et al 1999). Tricyclic antidepressants were associated with a higher proportion of reported side effects than were St John's wort preparations (47% *vs* 26.4%, respectively; relative risk: 1.72; 95% CI: 1.30 to 2.14). Despite the stringent inclusion criteria for trials in this meta-analysis, it was concluded that further studies are required to

address methodological problems before it can be concluded that St John's wort is an effective antidepressant (Kim et al 1999).

Several randomised, controlled trials of monopreparations of St John's wort involving patients with depressive disorders (Laakmann et al 1998; Schrader et al 1998, 2000; Philipp et al 1999; Harrer et al 1999; Brenner et al 2000; Woelk 2000) have been published since the Cochrane review (Linde & Mulrow 2001). Two trials compared St John's wort against placebo only (Laakmann et al 1998; Schrader et al 1998), others compared St John's wort with fluoxetine (Harrer et al 1999), sertraline (Brenner et al 2000), and imipramine (Woelk 2000), and one was a 3-arm study comparing St John's wort with imipramine and placebo (Philipp et al 1999).

In a randomised, double-blind, multicentre study, 162 patients with mild-to-moderate depression received St John's wort extract (ZE 117) 250 mg twice daily (equivalent to hypericin 1 mg daily), or placebo, for 6 weeks (Schrader et al 1998). 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. 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 (Laakmann et al 1998). Patients received St John's wort extract 300 mg (WS 5573, containing 0.5% hyperforin), 300 mg (WS 5572, containing 5% hyperforin), or placebo, three times daily for 6 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 hyperforin 0.5% and placebo recipients, respectively, were classified as responders. Proportions of patients reporting adverse events were similar (28.6% vs 28.6% vs 30.6% for hyperforin 5%, hyperforin 0.5% 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 (Laakmann et al 1998).

In a study comparing St John's wort with a selective serotonin reuptake inhibitor, 161 patients aged 60 to 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 6 weeks (Harrer et al 1999). 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 depression and moderate depression were analysed. 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 6 and 8 cases, respectively (Harrer et al 1999).

In another randomised controlled trial involving 240 patients with mild-to-moderate depression, St John's wort extract (ZE 117, ethanolic extract 50% w/w, drug-extract ratio 4–7:1) 250 mg twice daily was compared with fluoxetine 20 mg once daily, for 6 weeks (Schrader 2000). At the end of the study, St John's wort extract and fluoxetine were reported to be equipotent with respect to the main efficacy parameter (change in Hamilton Depression Scale score). The frequency of adverse events in hypericum- and fluoxetine-treated patients was 8 and 23%, respectively.

The effects of St John's wort extract (LI 160; 600 mg day^{-1} for one week followed by 900 mg day^{-1} for six weeks) were compared with another selective serotonin reuptake inhibitor, sertraline (50 mg daily for one week, then 75 mg daily for six weeks), in a randomised, double-blind trial involving 30 outpatients with mild-to-moderate depression (Brenner et al 2000). A clinical response, defined as $\geqslant$ 50% reduction in Hamilton Rating Scale for Depression scores, was observed in 40 and 47% of sertraline- and hypericum-treated patients, respectively. The difference between the groups was statistically non-significant, suggesting that the two agents were equivalent. However, it is important to note the small sample size, and that the calculation for statistical power was carried out post-hoc rather than before the study.

In the largest randomised, double-blind trial of St John's wort to date, 324 outpatients with mild-to-moderate depression received imipramine 75 mg twice daily (n = 167), or a 50% w/w ethanolic extract of hypericum (ZE 117, standardised to hypericin 0.2%) 250 mg twice daily (n = 157), for six weeks (Woelk 2000). The results indicated that hypericum extract ZE 117 and imipramine reduced Hamilton Depression Scale scores to a similar extent, compared with baseline values;

proportions of participants experiencing ⩾ 50% reduction in Hamilton Rating Scale for Depression scores were 40 and 43% for imipramine- and hypericum-treated patients, respectively. Adverse events were reported by 39 and 63% of hypericum and imipramine recipients, respectively. Of the 359 adverse events reported in total, 202 were thought to be possibly or probably related to treatment with one of the study drugs. Of these, 25% were reported by hypericum recipients and the remaining 75% by imipramine recipients.

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 to 0.3% hypericin and 2 to 3% hyperforin; n = 106), imipramine 100 mg daily (in 3 divided doses: 50 mg, 25 mg and 25 mg; titrated from 50 mg on day 1, 75 mg on days 2 to 4; n = 110), or placebo (n = 47), for 8 weeks (Philipp et al 1999). Hypericum was found to be more effective than placebo after 6 weeks of treatment, and to be as efficacious as imipramine after 8 weeks of treatment. Also, 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 did placebo. Adverse events were reported by 22% of St John's wort recipients, 46% of imipramine recipients, and 19% of placebo recipients.

This study has been 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 (Linde & Berner 1999). Nevertheless, this (Philipp et al 1999) and other new trials (Laakmann et al 1998; Schrader et al 1998) confirm that St John's wort extracts are more effective than placebo in mild-to-moderately severe depression (Linde & Berner 1999). 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 to 1800 mg daily) with the selective serotonin reuptake inhibitor sertraline (50 to 150 mg daily), in patients with major depression according to DSM-IV criteria, is ongoing in the United States (Vitiello 1999). Published abstracts of randomised, double-blind, controlled trials report superiority of St John's wort extract over placebo (Kalb et al 2000), and equivalent efficacy between St John's wort and fluoxetine 20 mg daily in mild-to-moderate depression (Friede et al 2000; Käufler et al 2000), and between St John's wort and imipramine 150 mg daily (Käufler et al 2000).

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 hypericin 1 mg (n = 119), 0.33 mg (n = 115) or 0.17 mg (n = 114) for 6 weeks (Lenoir et al 1999). At the end of the treatment period, there was a significant reduction in HAMD scores, compared with baseline values. Response rates (according to recognised criteria) were 68%, 65% and 62% for hypericin 1 mg, 0.33 mg and 0.17 mg, respectively; 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) (Kasper 1997; Wheatley 1999), 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 hypericin 0.9 mg) with or without bright light therapy (Kasper 1997). After 4 weeks, there were significant reductions in HAMD scores in both groups, compared with baseline values; 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 8 weeks (Wheatley 1999). The study was not randomised and involved data collection by postal questionnaires. Data from 301 returned questionnaires were suitable for analysis. Significant reductions in mean SAD scores were observed in both groups, compared with baseline values; differences in SAD scores between groups were statistically non-significant.

Antiviral activity

Antiviral activity has been reported for hypericin against HIV and hepatitis C (Anon 1995,a b). 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 (e.g. Cooper & James 1990; Steinbeck-Klose & Wernet 1993). In a phase I, dose-escalating study, 30 HIV-positive patients with CD4 cell counts < 350 cells/mm^3 received intravenous synthetic hypericin 0.25 or 0.5 mg kg^{-1} bodyweight twice weekly, 0.25 mg kg^{-1} three times weekly, or oral hypericin 0.5 mg kg^{-1}

daily (Gulick et al 1999). 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 titer, HIV RNA copies and CD4 cell counts was not observed.

Other conditions

The potential for the use of St John's wort in 20 individuals presenting with fatigue (Stevinson et al 1998) and in 19 women with self-reported premenstrual syndrome (Stevinson & Ernst 2000) has also been explored in uncontrolled pilot studies. Significant improvements in perceived fatigue and in symptoms of depression and anxiety were seen after 6 weeks' treatment with St John's wort (equivalent to 0.9 mg hypericin daily), compared with baseline values (Stevinson et al 1998), and in overall premenstrual syndrome scores after treatment with St John's wort (equivalent to 0.9 mg hypericin daily) for two menstrual cycles (Stevinson & Ernst 2000). In another open, uncontrolled pilot study, 12 individuals with obsessive–compulsive disorder of at least 12 months' duration received a fixed dose of an extended-release formulation of St John's wort (0.3% hypericin; 450 mg twice daily for 12 weeks) (Taylor & Kobak 2000). After treatment, significant improvements in Yale-Brown Obsessive Compulsive Scale scores were observed, compared with baseline values. Thus, there is scope for conducting randomised controlled trials of St John's wort in these conditions (Stevinson et al 1998; Stevinson & Ernst 2000; Taylor & Kobak 2000).

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 6 weeks (Boblitz et al 2000). The results indicated that the combination product had a significantly greater effect on symptoms than did placebo. Post-marketing surveillance studies have been carried out with extracts of St John's wort in patients with psychovegetative disorders (Mueller 1998a), and in women with menopausal symptoms of psychological origin (Grube et al 1999) [see *Safety aspects. Adverse effects: type and frequency*]. 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 8 days investigated the effects on quantitative electroencephalogram as an indicator of drug-induced pharmacological action (Schellenberg et al 1998). In both groups of St John's wort recipients, compared with placebo recipients, reproducible central pharmacodynamic effects were apparent. Effects were greater in subjects who received extract containing hyperforin 5.0% than in those who received extract containing hyperforin 0.5%.

Placebo-controlled, cross-over 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 REM sleep latency, compared with placebo, but had no effect on REM sleep duration or other parameters of sleep architecture (Sharpley et al 1998).

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 bodyweight than did subjects in placebo and no-treatment control groups (Colker et al 1999).

A placebo-controlled, cross-over 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 2 groups in sense of well-being or adverse events (Friede et al 1998).

A randomised, double-blind, placebo-controlled, 6-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 (Hottenrot et al 1997).

Safety aspects

Adverse effects: type and frequency

A review of safety data for St John's wort obtained from reports of randomised controlled trials, from drug monitoring and post-marketing surveillance studies (Albrecht et al 1994; Woelk et al 1994; Grube et al 1997; Meier et al 1997), and from national and international drug safety monitoring bodies has been published (Ernst et al 1998). 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 (Ernst et al 1998). Photosensitivity appears to be an extremely rare event with recommended doses of St John's wort (see below) (Ernst et al 1998).

Several post-marketing surveillance studies of the St John's wort extracts HYP811 (Mueller 1998a, b), LI 160 (Grube et al 1999; Holsboer-Trachsler et al 1999) and Neuroplant (Lemmer et al 1999) 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 to 6 weeks, although one study monitored 111 women for 12 weeks; Grube et al 1999). The frequency of adverse reactions in 6382 patients with mild depression who took St John's wort for 6 weeks was reported to be 0.125% (mainly skin reactions) (Lemmer et al 1999).

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 (Linde & Mulrow 2001). 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% vs 26.4%, respectively; Kim et al 1999). Randomised controlled trials (Laakmann et al 1998; Schrader et al 1998; Harrer et al 1999; Philipp et al 1999; Schrader 2000; Woelk 2000) published since the Cochrane meta-analysis (Linde & Mulrow 2001) and published abstracts (Friede et al 2000; Kalb et al 2000; Käufeler et al 2000) also report that St John's wort has a more favourable short-term safety profile than standard antidepressants (Harrer et al 1999; Philipp et al 1999; Friede et al 2000; Käufeler et al 2000; Schrader 2000; Woelk 2000), and that the frequency of adverse events seen with St John's wort is similar to that for placebo (Laakmann et al 1998; Schrader et al 1998; Philipp et al 1999; Kalb et al 2000). 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 (Harrer et al 1999). 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 (Ernst et al 1998). A review has attempted to compare systematically the safety profile of St John's wort with that of several conventional antidepressants (Stevinson & Ernst 1999).

Photosensitivity

Clinical observations. Sensitivity to sunlight following the ingestion of hypericum or hypericin is known as hypericism. Hypericin is stated to be the photosensitising agent present in St. John's wort (Durán & Song 1986).

Delayed hypersensitivity or photodermatitis has been documented for St. John's wort, following the ingestion of a herbal tea made from the leaves (Anon 1979). Three case reports document photosensitivity reactions in individuals who had used topical and/or oral St John's wort preparations prior to undergoing phototherapy or being exposed to the sun (Lane-Brown 2000).

In a double-blind, cross-over, single-dose study involving 13 healthy volunteers who received placebo, 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 h after dosing (Brockmöller et al 1997). In a multiple-dose study in which 50 volunteers received St John's wort (LI 160) 600 mg three times daily (equivalent to 5.62 mg total hypericin daily) for 15 days, a moderate increase in UV-A sensitivity was observed (Brockmöller et al 1997). Doses used were, however, 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^{-1} (Schempp et al 1999a). After administration of St John's wort 300 mg three times daily for 7 days to achieve steady state concentrations, the mean serum total hypericin concentration was 12.5 ng mL^{-1} and the mean skin blister fluid concentration was 2.8 ng mL^{-1}; these concentrations are below those estimated to be phototoxic (> 100 ng mL^{-1}) (Schempp et al 1999a).

A study reported that HIV-positive patients treated with oral hypericin 0.05 mg kg^{-1} 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^{-1} (Pitisuttithum et al 1996). In a dose-escalating study involving 30 HIV-infected patients treated with oral (0.5 mg kg^{-1} daily) or intravenous hypericin (starting dosage: 0.25 mg kg^{-1} twice or three times weekly), 16 patients discontinued treatment before completing 8 weeks of therapy because of moderate or severe phototoxicity; severe cutaneous phototoxicity was observed in 11 of 23 evaluable patients (Gulick et al 1999). 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.

In a study investigating the photosensitising capacity of topical St John's wort, volunteers (n = 8 for each preparation) applied hypericum oil (containing hypericin 110 μg mL^{-1}) or hypericum ointment (containing hypericin 30 μg mL^{-1}) to their forearms before exposure to solar-simulated radiation (Schempp et al 2000b). Visual assessment detected no change in erythema after application of either preparation, although evaluation of skin erythema using a more sensitive photometric measurement revealed an increase in erythema index after treatment with hypericum oil.

In-vitro and animal studies. The consumption of large quantities of St John's wort by grazing animals has been associated with the development of photosensitivity (Giese 1980). 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 LC50 (lethal concentration) with hypericin, but only a mild reduction with hypericum (Siegers et al 1993). From these findings it has been estimated that at least 30 times the therapeutic dose would be necessary to produce phototoxic effects in humans (Siegers et al 1993). 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 (Johnston 1999). An in-vitro study investigating the effects of hypericin (5×10^{-5} M), in the presence and absence of light, on lens alpha crystallin isolated from calf lenses found that, in the presence of light, oxidative changes occurred in alpha crystallin which increased with irradiation time (Schey et al 2000).

There are no reports of cataract formation in individuals who have taken St John's wort.

Other effects

Clinical observations. A case of subacute toxic neuropathy possibly related to use of St John's wort and subsequent exposure to sunlight has been reported (Bove 1998). A woman developed stinging pains in areas exposed to the sun (face and hands) 4 weeks after starting treatment with St John's wort 500 mg day^{-1} (extract and hypericin content not stated); the report did not state whether the woman was using any other products. Her symptoms improved 3 weeks after stopping St John's wort and disappeared over the next 2 months.

There have been reports of sensory nerve hypersensitivity occurring in individuals who had taken St John's wort preparations (tablets or tinctures) (Baillie 1997).

Cases of mania (Nierenberg et al 1999; Barbenel et al 2000) and hypomania (O'Breasil & Argouarch 1998; Schneck 1998) 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 (Nierenberg et al 1999), and one in a patient experiencing a moderate depressive episode who was taking both sertraline and St John's wort (dosage not known) (Barbenel et al 2000). 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 (Schneck 1998). Two cases of hypomania were reported in individuals with no history of bipolar disorder (O'Breasil & Argouarch 1998). 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 6 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 3 months of self-treatment with St John's wort (dosage not stated) (O'Breasil & Argouarch 1998).

Several of these reports stated that 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 (O'Breasil & Argouarch 1998). None of the cases involved rechallenge with St John's wort and in all cases there were other pharmacological factors and/or underlying illness that could have been responsible for or contributed to the precipitation of mania.

In-vitro and animal studies. Experimental studies investigating the genotoxic potential and mutagenic activity of St John's wort extracts in-vitro and in-vivo have been summarised (ESCOP 1996; *American Herbal Pharmacopeia* 1997). In-vivo studies and most in-vitro studies provided negative results, indicating a lack of mutagenic potential with defined St John's wort extracts (ESCOP 1996). 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 car-

cinogenicity of quercetin in humans (ESCOP 1996; *American Herbal Pharmacopeia* 1997).

The effects of St John's wort on sperm motility have been investigated in an in-vitro study involving the incubation of St John's wort with washed sperm (Ondrizek et al 1999). Sperm motility was reported to be inhibited at the highest concentration (0.6 mg/mL) of St John's wort investigated.

Dietary administration of St. John's wort to rats was found to have no effect on various hepatic drug metabolising enzymes (e.g. aminopyrine, *N*-demethylase, glutathione *S*-transferase, epoxide hydrolase) or on copper concentrations in the liver [*see* 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, 5% thereafter because of unpalatability) (Garrett et al 1982).

Pregnancy and lactation

There is a report of a 38-year-old woman who started taking St John's wort 900 mg day^{-1} at her 24th week of pregnancy, taking the last dose 24 h before delivery (Grush et al 1998). 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^{-1}. The report does not state the outcome of the pregnancy (Grush et al 1998), although it is assumed that had adverse events occurred, they would have been stated.

Slight in-vitro uterotonic activity in guinea pigs and rabbits has been reported for a crude aqueous extract of St. John's wort (Shiplochliev 1981).

In view of the lack of toxicity data, St. John's wort should not be used during pregnancy and lactation.

Drug interactions

It has previously been suggested that excessive doses of St John's wort may potentiate MAO inhibitor therapy (Newell et al 1996). However, as MAO inhibitory activity has not been reported in-vivo with St John's wort, this warning is no longer considered necessary. Also, avoidance of foodstuffs, such as those containing tyramine (eg. cheese, wine, meat and yeast extracts), and medicines containing sympathomimetic agents (eg cough/cold remedies), which interact with MAO inhibitors is not considered necessary whilst taking St John's wort.

Recent evidence has emerged from spontaneous reports (Yue et al 2000) and published case reports (Rey & Walter 1998; Nebel et al 1999; Barone et al 2000; Breidenbach et al 2000; Piscitelli et al 2000; Ruschitzka et al 2000) of interactions between St John's wort and certain prescribed medicines, leading to a loss of or reduction in therapeutic effect of these prescribed medicines. Drugs that may be affected include indinavir, warfarin, ciclosporin, digoxin, theophylline and oral contraceptives. There have also been other reports of increased serotonergic effects in patients taking St John's wort concurrently with selective serotonin reuptake inhibitors (eg sertraline, paroxetine) (Gorden 1998; Lantz et al 1999).

Drug-interaction studies in healthy volunteers have provided supporting evidence of interactions between St John's wort and phenprocoumon (Maurer et al 1999) and digoxin (Johne et al 1999), and have provided evidence that St John's wort may induce some cytochrome P450 (CYP) drug metabolising enzymes in the liver (Maurer et al 1999; Kerb et al 1997; Roby et al 2000), namely CYP3A4, CYP1A2 and CYP2C9, as well as affecting P-glycoprotein (a transport protein). In-vitro studies have reported that crude extracts of St John's wort inhibit CYP2D6, CYP2C9, CYP3A4, CYP1A2 and CYP2C19 enzyme activity, and that hyperforin is a potent noncompetitive inhibitor of CYP2D6 activity and a competitive inhibitor of CYP2C9 and CYP3A4 activity (Obach 2000). It has also been shown that treatment of human hepatocytes with hypericum extract and hyperforin results in a marked induction of CYP3A4 expression, and that hyperforin is a potent ligand for the pregnane X receptor, a nuclear receptor that regulates the expression of CYP3A4 monooxygenase (Moore et al 2000). By contrast, some studies involving volunteers have failed to find significant effects on CYP isoenzymes (Ereshefsky et al 1999; Gewertz et al 1999; Markowitz et al 2000), although numbers of volunteers may have been too small and the duration of St John's wort administration too short to truly exclude an inductive effect (Gewertz et al 1999; Markowitz et al 2000). Against this background, and since the content of active constituents can vary between different preparations of St John's wort, the degree of enzyme induction may vary.

These concerns 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 (Anon 2000; Breckenridge 2000). The CSMs' advice for health-care professionals for patients taking St John's wort and certain drugs is summarised below. Patients already taking any of the drugs listed should be advised not to start taking St John's wort; users of other medicines should be advised to seek professional

Table 1 Reports of suspected interactions between St John's wort and conventional drugs received by the UK Committee on Safety of Medicines for the period October 1996 to September 2000†.

Drug(s)	Reports (n)	Comment
Warfarin	4	Increased INR (2 reports) Decreased INR (2 reports)
SSRIs	4	Paroxetine (3 reports) Sertraline (1 report)
Theophylline	1	Reduced serum theophylline concentration
Indinavir, lamivudine, stavudine	1	HIV viral load increased
Tacrolimus	1	Drug ineffective
Oral contraceptives	11	Intermenstrual bleeding (6 reports) Unintended pregnancy (5 reports)
Other drugs	13	Including: sodium valproate (1 report), zuclopenthixol (1 report), atorvastatin (1 report), moclobemide (1 report), verapamil (1 report), lithium (1 report), thyroxine (1 report)

†Source: Medicines Control Agency Adverse Drug Reactions Online Information Tracking (ADROIT)
INR, international normalised ratio; SSRIs, selective serotonin reuptake inhibitors

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. Also, topical or homoeopathic preparations of St John's wort are not likely to interact with prescribed medicines.

The UK Committee on Safety of Medicines (CSM) and Medicines Control Agency have received 35 reports of suspected interactions between St John's wort and conventional medicines over the period October 1996 to September 2000. In several cases, the individuals concerned were taking other (conventional) drugs. The reports are summarised in Table 1. Interactions between preparations of St John's wort (*Hypericum perforatum*) and conventional drugs, compiled from information circulated by the UK Committee on Safety of Medicines (Breckenridge 2000), are presented below.

Warfarin, *ciclosporin*, *digoxin*, *theophylline*, *anticonvulsants* (*carbamazepine*, *phenobarbitone*, *phenytoin*). There is a risk of reduced therapeutic effect, eg risk of transplant rejection, seizures, loss of asthma control. Advice is to check plasma drug concentrations (with warfarin, the patient's INR should be checked), and to stop St John's wort therapy. Also, dose adjustment may be necessary.

HIV protease inhibitors (*indinavir*, *nelfinavir*, *ritonavir*, *saquinavir*), *HIV non-nucleoside reverse transcriptase inhibitors* (*efavirenz*, *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*, *zolmitriptan*), *selective serotonin reuptake inhibitors* (*citalopram*, *fluoxetine*, *fluvoxamine*, *paroxetine*, *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.

Comment

St John's wort preparations are widely available in several formulations (eg tablets, tinctures, topical preparations) from pharmacies, health-food stores and from herbal medicine practitioners, and are among the top-selling herbal products in Western countries. A small study carried out in the US revealed that one of the main reasons for consumers' use of St John's wort rather than prescription antidepressants is the belief that St John's wort is natural and safer, and has fewer adverse effects than conventional antidepressants; other reasons include accessibility, and lack of effectiveness or tolerability of conventional antidepressant agents (Beckman et al 2000).

St John's wort products are usually standardised on hypericin (Figure 2) content, as this constituent was originally thought to be responsible for St John's wort's antidepressant effects. It has now emerged that hyperforin (Figure 1) is one of the major constituents responsible for antidepressant activity, although further research is required to determine which other constituents contribute to the antidepressant effect. As hyperforin is unstable (Verotta et al 2000), standardising products on hyperforin content is problematic.

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 (Linde & Mulrow 2001). 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 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; recent studies have compared St John's wort with fluoxetine and with sertraline. Also, generally there is 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. St John's wort does appear to have a more favourable short-term safety profile than do standard antidepressants, a factor that is likely to be important in patients continuing to take medication.

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 (*American Herbal Pharmacopeia* 1997). Topical hypericum preparations do not appear to have a severe phototoxic potential, although increased photosensitivity may be important in fair-skinned individuals, and in those with diseased skin (Schempp et al 2000b).

Concerns have been raised over interactions between St John's wort and certain prescribed medicines (including warfarin, ciclosporin, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, triptans, oral contraceptives); advice is that patients taking these medicines should stop taking St John's wort, generally after seeking professional advice as dose adjustment of conventional treatment 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 remedies, without first seeking professional advice.

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