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Efficacy and safety of St. John's wort for the treatment of major depression

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Abstract

Objective: Extracts of St. John's wort have been widely used in the treatment of depression. Our aim was to review information related to the efficacy and safety of St. John's wort as an antidepressant.

Data sources: Primary and review articles were identified by a search of Medline (1960 to February 2000) and through secondary sources.

Study selection: All the articles identified from the data sources were evaluated and all relevant information was included in this review. The pharmacokinetics, mechanism of action, efficacy, side effects and drug interactions of St. John's wort have been examined in various studies.

Conclusion: St. John's wort is a promising investigational antidepressant, but the data are not yet sufficient to accept hypericum as a first line antidepressant preparation for treatment of depression. Besides the need for dose standardization and adequate trial lengths, there is a need for studies in severely depressed patients and long-term studies to assess the risk of relapse and recurrence.

Keywords
Hypericum
Major depression
Clinical trials
Adverse events
Drug interactions
Hyperforin

Major depressive disorder (MDD) is one of the most common serious illnesses worldwide with a lifetime prevalence of 17%[1]. It remains a leading cause of psychiatric morbidity and psychosocial disability. Unfortunately, MDD is still under-recognized and under-treated. The stigma of mental illness and lack of access to mental health care, as well as misperceptions about the side effects of antidepressants, contribute to this problem[2]. MDD is a chronic illness and there is a 50% recurrence rate after one episode of depression and 80% recurrence rate after two episodes in untreated patients.

MDD is a syndrome and is currently diagnosed using the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria. To meet criteria for MDD, a patient must have either a depressed mood or loss of interest in almost all activities every day for at least a 2-week period plus five or more supporting signs and symptoms of depression (e.g. sleep disturbance). These feelings must result in functional and/or social impairments. The differential diagnosis of MDD consists of other mood disorders such as bipolar disorder, dysthymia, minor depression as well as mood disorders secondary to medical conditions (e.g. stroke).

The exact cause of MDD as well as the mechanism of action of antidepressants is still unknown. One theory suggests that MDD results from a deficiency of serotonin and/or norepinephrine. Effective treatments for MDD include pharmacotherapy, phototherapy, psychotherapy (e.g. cognitive behavioural therapy) or combinations of the above. There are over 20 different antidepressant medications that belong to one of eight pharmacological classes. The tricyclic antidepressants (TCAs) are still used widely among general practitioners though concerns about their safety in overdose, cardiac effects and other side effects have led to a decline in their popularity. The selective serotonin reuptake inhibitors (SSRIs) are currently viewed as first line agents primarily because of a superior tolerability profile. All antidepressant medications on the market today are believed to have similar efficacy and clinicians choose medications primarily based on side effect profiles. Because of the chronic nature of depression, current guidelines call for continuation of antidepressant therapy for at least 4 to 9 months (continuation phase) after full initial response (acute phase) to prevent relapse. In addition, patients with risk factors (e.g. previous history of recurrent depression) may also require extended treatment for years (maintenance phase) to prevent recurrences. Prescription agents have been studied in 1- to 2-year trials of MDD and proven effective in reducing the rates of relapse and recurrence in MDD.

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Alternative therapy

Alternative treatment approaches for MDD include exercise, yoga, meditation, biofeedback and herbal remedies. In this article, we will primarily focus on the use of St. John's wort (SJW), a herbal extract, for the treatment of MDD.

Historical perspective on St. John's wort

St. John's wort (*Hypericum perforatum*) has been used as a medicinal herb since ancient times. The word 'hypericum' is derived from the Greek and translates as 'above' and 'icon'. It was usually harvested on June 24th (St. John's day) and reportedly used as a shield against evil spirits. It was later used for a variety of medicinal purposes, such as the treatment of ulcers and tumours, as a diuretic, and for the treatment of nervous and psychiatric disorders like insomnia or overactivity of the mind[3]. This herb was traditionally consumed in the form of a tea containing an aqueous extract, a single dose of which corresponded to 2–3 g of the dried crude drug[4]. The herb was permitted to grow wild in many countries until the late 1800s, when reports appeared of phototoxicity in fair-skinned animals after ingestion of SJW. This led to attempts in the US and Australia to eradicate SJW.

More than 370 hypericum species exist worldwide. Twenty-five species are found in North America. Native to Europe, North Africa and western Asia, *Hypericum perforatum* now grows wild in parts of Africa, Asia, Australia, and the Americas[3,5]. The current popularity of SJW can perhaps be traced to the 1990s with the publication of several influential reviews as well as promotional activities undertaken by herbal supplement manufacturers. SJW is a popular antidepressant in many European countries and is available by prescription in Germany. In the United States, SJW is regulated as a dietary supplement. In 1998, worldwide sales of SJW were estimated to be US$570 million and US sales to be $210 million. SJW sales are estimated to be growing at approximately 50–90% per year in the last few years compared with an approximate 20% growth rate for the SSRIs.

Chemical constituents

Chemical components of SJW include napthodianthrones (0.05–0.15%): hypericin and pseudohypericin, protohypericin, protopseudohypericin and cyclopseudohypericin. It also contains tannins and proanthocyanidins (6–15%), flavonoids (2–5%), phloroglucinol derivatives (up to 4% hyperforin), phenolic acids, coumarins, monoterpenes, sesquiterpenes, sterols, vitamins C and A, xanthones, choline and volatile oils (0.05–1%): *n*-alkanes and *n*-alkones[5]. There is still a lack of consensus about which of the above ingredients are responsible for SJW antidepressant activity. Some data suggest that hypericin is the active ingredient and other evidence suggests that hyperforin is the active ingredient. It is likely that, as with many other herbal extracts, a combination of ingredients could be responsible for biological activity. Hypericin remains intact through ingestion, digestion, absorption into the blood stream, and passage through the liver. The psychotropic effects of hypericin suggest that it can cross the blood–brain barrier. Variability of chemical constituents has been found in various commercial extracts of the herb. This is a potential source of unpredictability in clinical response across different commercial preparations of SJW extracts.

Pharmacokinetics

Pharmacokinetic studies have been performed with a SJW extract known as LI 160 (Lichtwer Pharmaceutical preparation) which contains 300 mg of dried extract of *Hypericum perforatum* with 0.24–0.32% hypericins. This preparation was orally administered to 12 healthy subjects at single doses of 300, 900 and 1800 mg. Plasma concentrations peaked after 2–2.6 h with hypericin and 0.4–0.6 h with pseudohypericin. The peak concentrations for hypericin were 1.5, 7.5 and 14.2 ng ml^{-1}, respectively, for the 300, 900 and 1800 mg doses and 2.7, 11.7 and 30.6 ng ml^{-1} for pseudohypericin[6]. The half-life of hypericin is reported as approximately 25 h although in practice the extract is usually dosed three times a day. Plasma levels of hyperforin were measured by Biber *et al.* for up to 24 h in healthy volunteers who were administered a 300-mg single dose of hypericum extract containing 14.8 mg hyperforin. A maximum plasma level of approximately 150 ng ml^{-1} was reached 3.5 h after administration. Its half-life was 9 h. Results from a repeated dose study estimated the steady state plasma concentration of hyperforin to be 100 ng ml^{-1} with $3 \times 300\,mg\,day^{-1}$ of hypericum extract[7].

Mechanism of action

Little is known about the putative mechanism of action of SJW in depression. Several possible mechanisms have been suggested. Although some MAO inhibition (MAOI) has been demonstrated *in vitro*, this effect has not been observed *in vivo*. There have been no cases of MAOI-associated hypertensive crisis in humans using SJW[8]. In a recent study, the *in vitro* effects of LI 160 on MAO-A and MAO-B activity were investigated using mouse brain homogenates and C-serotonin and C-b-phenylethylamine probes. IC_{50} concentrations of LI 160 were 120 $\mu g\ ml^{-1}$ for MAO-A and 370 $\mu g\ ml^{-1}$ for MAO-B. This study suggested that the potency of LI 160 for inhibiting MAO-A and MAO-B activities was too weak to be of clinical relevance at usually administered doses in MDD. Hypericum extract may interfere with presynaptic serotonin uptake with an IC_{50} of 2.4 $\mu g\ ml^{-1}$. A reversible 50% decrease in the rate of serotonin transport has also been recorded. It also inhibits

norepinephrine reuptake with IC_{50} of 4.5 μg ml^{-1} and dopamine reuptake with IC_{50} 0.9 μg ml^{-1} (see Ref. 9). The concentrations required to reach these effects is quite high and hence the clinical significance is not known.

Muller and Rossol incubated neuroblastoma cells with hypericum extract LI 160 in kinetic form and found reduced expression of serotonin receptors compared with a placebo solution[10]. Teufel and Gleitz demonstrated up-regulation of 5-hydroxytryptamine-1 A (5HT1 A) and 5HT2 A receptors after prolonged administration of hypericum extracts (2700 mg kg^{-1} LI 160 for 26 weeks) to rats, similar to the expression levels of these receptors by synthetic antidepressants. These results emphasize the importance of serotonin in the antidepressant action mechanism of hypericum[11].

Hypericin may also affect activity at GABA receptor level. The effect at the GABA-A receptor subtype is shown with an IC_{50} of 75 ng ml^{-1} and that at the GABA-B receptor is seen at 6 ng ml^{-1} which is the most potent effect reported to date[8]. Flower extracts of *Hypericum perforatum* with an IC_{50} value of 6.83 have been found to efficiently inhibit the binding of [3H] flumazenil to benzodiazepine binding sites of GABA-A receptor in rats with an IC_{50} value of 6.83[12].

In 1998, Raffa studied the affinity of hypericin (1.0 μM) for muscarinic cholinergic and sigma receptors. They found 49% inhibition of muscarinic and 48% inhibition of sigma receptors. This is a significant finding considering sigma receptors have been associated with the antidepressant action of synthetic agents and are located in the limbic system, which is implicated in the regulation of emotions. It has been postulated that sigma receptors modulate NMDA-glutamate receptors, which is an important pathway for antidepressant action[13].

Other proposed mechanisms are interleukin-6 inhibition, beta-adrenoceptor down-regulation and increase in levels of endorphins or melatonin[14]. It has been postulated that a combined contribution of several of these mechanisms could be responsible for the clinical efficacy of SJW, each one too weak by itself to contribute to the overall effect[15].

Although hypericin has long been considered the active ingredient responsible for antidepressant activity, studies have not yet confirmed this hypothesis. The antidepressant effects of this herb may also theoretically be due to several compounds in combination. In a recent survey, flavonoids along with hypericins were found to be most biologically active[16]. Chatterjee *et al.* reported that hyperforin, the phloroglucinol derivative, is a possible major active principal responsible for the antidepressant activity[17]. Hyperforin is a major lipophilic constituent of SJW and also a relatively potent reuptake inhibitor of serotonin, dopamine, noradrenaline, GABA and L-glutamate[17,18]. In a randomized, double-blind study, 147 patients with mild to moderate depression were allocated to one of three treatment groups: placebo, hypericum extract WS 5573 (300 mg, with 0.5% hyperforin) and WS 5572 (300 mg, with 5% hyperforin). At the end of the 42-day treatment period, patients receiving WS 5572 exhibited higher response rates on Hamilton Depression Rating Scale (HAMD) scores than the WS 5573 group and both groups had better response rates than placebo. These results suggest that the antidepressant effect of SJW may be associated with the hyperforin content[19]. In 1998 Muller *et al.* identified hyperforin as a nonspecific reuptake inhibitor of serotonin, norepinephrine, and dopamine at concentrations between 80 and 200 nmol l^{-1}, leading to down-regulation of cortical beta-adrenoreceptors and 5HT2 receptors with subchronic treatment. This suggests hyperforin to be the active component of hypericum extracts involved in antidepressant activity[20]. In another study, Chatterjee *et al.* investigated the inhibition of GABA, AMPA and NMDA conductance by hyperforin in hippocampal and cerebellar neurons of rats. The AMPA induced current was inhibited by hyperforin in a competitive manner, requiring a very high concentration of the agent. However, NMDA receptor-activated ionic conductance was completely and uncompetitively blocked, reconfirming hyperforin as a major neuroactive component of hypericum extracts[21]. Kaehler *et al.* suggested that increased concentration of monoamines and glutamate in the synaptic cleft, as a consequence of uptake inhibition by hyperforin, may be the mechanism of antidepressant action of SJW. They found enhanced catecholamines, serotonin and glutamate in the rat locus coeruleus, which has been implicated as an important area for antidepressant activity[22].

There have been several lines of evidence implicating other areas of the brain associated with antidepressant mechanisms of hypericum. In a study conducted in mice[23], Yu found hydroxyindoleacetic acid (5-HIAA) levels to be significantly increased in the cerebral cortex, hypothalamus, hippocampus and caudate 3 h after treatment with hypericum extract at a dose as low as 10 mg kg^{-1}. 5-HT levels were increased in the hypothalamus and hippocampus, areas known to be associated with depression. However, no change in MAO activity was found in mouse brain following either acute or chronic treatment with hypericum[23]. Calapai *et al.* demonstrated a significant dose-dependent 5-HT and 5-HIAA increase at the diencephalic level and an increase in noradrenaline in the brain stem after administration of hypericum extracts containing more flavonoids. These findings suggest the importance of flavonoids in antidepressant activity and also that the brain stem could be a target for the action of hypericum[24].

Hypericum may also increase growth hormone and decrease plasma prolactin, though the significance of these changes remains unknown. Plasma cortisol levels were found to be unchanged with hypericum[25].

Efficacy for MDD

SJW has been studied for the treatment of several conditions including MDD, anxiety syndromes, premen-

Table 1 Selected meta-analyses investigating the efficacy and safety of St. John's wort as a treatment for depression

First author	Year	Design	No. of trials or sample size	Main outcome	Response rates
Linde	1996	Meta-analysis	1575 patients in 23 trials	SJW superior to placebo and TCAs*	Placebo 22.3%, SJW 55.1% Single SJW extract 63.9% Antidepressants 58.5% Combination SJW 67.7%
Kim	1999	Meta-analysis	6 trials	SJW superior to placebo	SJW = antidepressants > placebo (1.5 times)
Linde	1999	Meta-analysis	27 trials, 2291 patients	SJW superior to placebo	
Gaster	2000	Meta-analysis	8 trials	SJW superior to placebo	TCAs ≥ SJW > placebo

* TCAs, tricyclic antidepressants.

strual syndromes and seasonal affective disorder (SAD). This article reviews only the data relevant to MDD.

In 1996, Linde *et al.* conducted a systematic review and meta-analysis of trials that examined the antidepressant activity of SJW (Table 1). Using their chosen criteria for appropriateness, 23 randomized trials of 1757 patients with mild to moderately severe depressive disorders were included in the analyses. Of these, 15 trials compared preparations of SJW (alone or in combination with other plant extracts) with placebo and eight trials compared SJW with other antidepressants. The most consistently used instruments were the HAMD and the Clinical Global Impression (CGI) index. The methodological quality of each trial was assessed by two reviewers using the Jadad scale as well as one by Linde *et al.*[26]. In the SJW vs. placebo comparison, the placebo response rate was 22.3% and the SJW response rate was 55.1%. In the hypericum vs. antidepressant comparison, the response rates were 63.9% for the single hypericum preparation vs. 58.5% for standard antidepressants. The response rate was 67.7% for those using SJW combination plant extracts. The daily dose of hypericin and total extract varied from 0.4 to 5.4 mg and from 300 to 1800 mg, respectively. Overall, the analyses and the accompanying editorial suggested that SJW is a promising investigational agent for the treatment of MDD. Possible limitations of the trials included in this meta-analysis are the inclusion of patients with heterogeneous levels of depression, less stringent application of inclusion and outcome criteria, short duration of treatment, use of subthreshold doses of standard antidepressants, pooling of studies done at specialist and primary care clinics, and pooling of the various extracts of SJW.

To address some of the issues raised by this report, a subsequent meta-analysis of six randomized double-blind trials comparing hypericum with placebo and standard prescription antidepressants was performed by Kim *et al.* in 1999[27]. They included subjects with similar sociodemographic backgrounds, who had depressive disorders defined by either International Classification of Diseases (ICD-10) or DSM IIIR, or DSM-IV criteria. HAMD scores were calculated at a variety of different intervals. Trials that used hypericum combinations were excluded. The results of this analysis showed that SJW was approximately 1.5 times more likely than placebo to improve depression (in contrast to the analysis by Linde *et al.*, in which SJW showed an almost three-fold improvement). The HAMD scores in both the SJW and antidepressant groups showed similar levels of improvement.

In 1999, Linde *et al.* updated their 1996 review by including 27 trials and 2291 patients with similar inclusion criteria[28]. Hypericum preparations were found to be significantly superior to placebo and as effective as standard antidepressants. Of the patients treated with SJW, 26.3% reported side effects compared with 44.7% of those treated with a standard antidepressant.

A more recent systematic review was conducted by Gaster and Holroyd[2]. This review included eight studies with high methodological quality using hypericum extract alone and reported that the efficacy of hypericum was 23–55% higher than placebo on the 21 item HAMD. However, the response rate was 6–18% lower than with tricyclic antidepressants. The average dose of the tricyclics was found to be lower than that generally used in psychiatric clinical practice. In contrast, in a trial by Wheatley, the response rate to amitriptyline at 75 mg day^{-1} was higher than that of hypericum[29]. Holsboer-Traschsler and Vanoni studied 647 patients with mild to moderate depression who were receiving hypericum extract. Using the von Zerssen depression score, symptoms of depression lessened in 75% of the patients, with the first signs of improvement at week 3 and further improvement at week 6. The severity of depression did not appear to have an effect on the outcome. However, the rate of improvement was slower in patients older than 65 years. Tolerance was reported as satisfactory in 89% of patients[30].

Recently, SJW extract has been compared with fluoxetine in the treatment of mild to moderate depression. The study included 240 patients with a HAMD (21 item) score in the range 16–24. After 6 weeks of treatment, mean HAMD score decreased to 11.54 for patients on SJW and to 12.20 for those on fluoxetine. Responder rate on the basis of Clinical Global Impression Severity score was found to be superior for SJW[31]. In another study that compared fluoxetine with SJW extract, LoHyp-57, in 72 patients with

mild depressive episodes and 77 patients with moderate depressive episodes, both drugs were found to be equally efficacious using HAMD-17[32]. Volz and Laux had similar results in their overview of nine controlled trials with fluoxetine and 17 with SJW. Studies with a HAMD score of 24 or less were included. The authors did not find any difference in the efficacy of the drugs in the treatment of mild to moderate depression. However, the analysis was not free of methodological flaws. There was a wide variation in the number of patients in the individual studies. SJW studies used different extracts and lacked single-blind placebo washout periods. However, thorough evaluation of these studies revealed good tolerability for SJW, representing an advance in the treatment of depression[33]. Two more recent studies of SJW have found somewhat conflicting results. In a carefully randomized trial[52], SJW was as effective as imipramine but better tolerated. In another trial, the first to be carried out in the US, SJW was equivalent to placebo and not effective (unpublished data) in a sample of 200 patients with MDD.

Kaspar compared a combination of SJW extract and bright light therapy with a combination of SJW and low intensity light (placebo) administered to patients suffering from SAD. The results suggested that SJW alone may achieve a similar efficacy to that of the combination[34]. These data seem to be confirmed by another study that found that Kira (a hypericum preparation) in monotherapy produced significant relief of SAD symptoms and that the addition of light therapy did not cause further significant improvement[35].

Despite the abundance of short-term trials, the efficacy of SJW has not yet been studied systematically in patients with psychotic depression, geriatric depression (where response rate may be lower and delayed), bipolar depression (where the primary treatment is mood stabilizer and there is a risk of increased mania with some antidepressants), premenstrual dysphoric disorder, dysthymia or double depression. The use of relatively small doses of tricyclic antidepressants may also have confounded prior comparisons. SJW has also to our knowledge not yet been compared with newer antidepressants, dual agents (e.g. venlafaxine) and noradrenergic agents (e.g. bupropion SR and reboxetine). Most hypericum studies have been performed with different SJW extracts. Data on the composition of these extracts, in relation to different constituents, are lacking. With the knowledge that some extracts are more efficacious than others, this limitation could be very significant. Thus, results that show the mean antidepressant effect do not necessarily reflect the antidepressant potential of an individual extract. The published data indicate that an optimal dose for acute treatment of milder varieties of depression may be 300 mg taken three times a day with increases up to 1800 mg day^{-1} based on clinical judgement. Since SJW is not indicated for the treatment of MDD in the US, we cannot make any recommendations with regards to dosing or use for the acute treatment of MDD in clinical practice. Further, to the authors' knowledge, SJW has not been systematically studied in order to evaluate its efficacy for the prevention of relapse or recurrence. Hence, no recommendations can be made as to its long-term efficacy.

Thus, these data suggest that SJW is a promising investigational antidepressant, but the data are not yet sufficient to accept hypericum as a first line antidepressant preparation for treatment of MDD. Besides the need for dose standardization and adequate trial lengths, there is a need for studies in severely depressed patients and long-term studies to assess the risk of relapse and recurrence. There is also a need to compare SJW with cognitive behavioural therapy and interpersonal therapy in MDD.

Adverse effects

In a large study involving 3250 patients, the most frequently reported adverse drug reactions were gastrointestinal symptoms (0.6%), allergic reactions (0.5%), and fatigue (0.4%). Only 1.1% of patients discontinued hypericum due to side effects. No serious adverse events were detected[36]. Likewise, seven randomized comparative studies of hypericum and other antidepressants including a total of 797 patients showed that the incidence of adverse effects in patients taking hypericum was less than 50%, whereas the incidence of adverse events with other antidepressants ranged from 32 to 103%. The most frequent events reported were gastrointestinal symptoms (8.5%), dizziness (4.5%), fatigue/sedation (4.3%) and dry mouth (4%). The other symptoms reported were restlessness, headaches, insomnia, tremor, pruritis, photophobia, apathy and allergic skin reactions[37].

Recently, Moses *et al.* reported three cases of possible treatment-emergent mania shortly after exposure to SJW in a spectrum of patients with diagnoses of unipolar depression, bipolar II and bipolar I disorders[38].

In a randomized, double-blind, parallel group study by Schrader, in which hypericum was compared with Fluoxetine in the treatment of mild to moderate depression, 23% of subjects on Fluoxetine reported adverse events, while the incidence of adverse events in patients on SJW was 8%. Patients on Fluoxetine reported agitation, GI disturbances, retching, dizziness, tiredness, anxiety/nervousness and erectile dysfunction. Patients on hypericum reported only GI disturbances. These results suggest that hypericum has a superior safety profile[31].

In a systematic review by Gaster and Holroyd, five of eight randomized trials carried out frequent laboratory monitoring of the 386 enrolled subjects. No changes were found in the complete blood count and in liver and kidney function tests related to SJW[2]. There are also several case reports and anecdotal reports of adverse effects due to SJW. One case of severe sedation has been reported in an elderly subject who started hypericum (600 mg day^{-1}) after

discontinuing paroxetine (40 mg day^{-1}) and then took 20 mg paroxetine 10 days later, while he was on hypericum[39].

The risk of photosensitivity associated with SJW in fair-skinned people and in those on high doses of the extract has been the subject of much discussion. Some photosensitivity has been demonstrated in a controlled four-fold double-blind clinical trial involving placebo or 900, 1800 or 3600 mg of LI 160 and exposure to UV irradiation. When 13 volunteers were given a single dose of placebo or hypericum, no increase in sensitivity to solar light was observed after 4 h. The sensitivity to UV rays marginally increased only with the highest dose (3600 mg). No correlation was found between total hypericin plasma concentrations and photosensitivity. However, when 50 volunteers received multiple doses of hypericum (600 mg, t.i.d.), UV light sensitivity increased slightly after 15 days of treatment[40]. One case of acute neuropathy was reported in a woman who had been taking SJW for 4 weeks before she developed the stinging pain on the face and hands after exposure to the sun[41]. In 1999, Bernd *et al.* confirmed the phototoxic effect of hypericin extract using cultures of human keratinocytes and comparing it with psoralen (a well known phototoxic agent). However, they felt that the blood levels of hypericin resulting from treatment of depression are too low to induce phototoxic skin reactions[42]. In addition, experimental studies are also examining the effects of SJW on skin pigment changes as well as on cataract formation. Phototoxicity in humans may be manifested as itchy, erythematous lesions and in the absence of reliable information on the true incidence rates of this potential side effect, it may be prudent to caution users.

In a study that compared the electrocardiographic effects of high-dose hypericum extract with imipramine hydrochloride, it was found that it was safe to use high dose hypericum with regard to cardiac function in elderly patients or in patients with pre-existing conductive dysfunction[43].

A toxicity study using dietary administration of hypericum to rats found no adverse effects on the liver or any significant tissue lesions. In a 26-week study performed in rats and dogs with oral doses of 900 and 2700 mg kg^{-1} of LI 160 (hypericum), only non-specific symptoms of toxicity were seen, including reduced body weight, slight pathological changes in the liver and kidneys from large metabolic load, and some histopathological changes in the adrenal glands. There were no effects on fertility or reproduction[44].

Few systematic studies have examined the effects of SJW on body weight and sexual function as well as potential effects related to abrupt discontinuation. In addition, there are only anecdotal reports of SJW use in pregnancy or during lactation and systematic pregnancy registry data (as are available with Fluoxetine) are not available to examine the effects on the foetus.

Drug interactions

In general, most drug interactions are well tolerated by patients and are often undetected in practice. While SJW appears to be relatively well tolerated, eight case reports suggest that it can induce hepatic enzymes. All eight patients were women receiving theophylline, cyclosporin, warfarin or oestrogen preparations (all these drugs are metabolized by cytochrome P450 microsomal oxidase enzymes) together with hypericum extracts. The plasma concentrations of all these drugs were found to be reduced[45]. Since 1998, the Medical Product Agency in Sweden has received seven case reports of a reduced anticoagulant effect of warfarin with concomitant use of SJW. They also received eight reports of intermenstrual bleeding and one report of changed menstrual bleeding in patients on oral contraceptives after starting SJW. This suggests an induction of CYP3A4 by SJW[46]. Many prescription drugs used to treat conditions such as heart disease, depression, seizures, certain cancers, or to prevent pregnancy (oral contraceptives) are metabolized via this enzyme pathway, and caution should be used to prevent loss of the therapeutic effect of these drugs when combined with hypericum.

A recent study also reported increased hepatic clearance and reduced plasma levels of indinavir (a protease inhibitor) on average by 57% and up to nearly 100%, suggesting CYP3A4 induction as the mechanism for the decrease in indinavir exposure, although effects on P-glycoprotein cannot be ruled out[47]. Hence, there is a theoretical possibility that SJW could also lead to reduced efficacy of some HIV regimen. However, in a recent study by Markowitz, the effects of hypericum on the activity of cytochrome P-450 (CYP) 2D6 and 3A4 were assessed in seven normal volunteers. It was found that at doses used to treat depression, hypericum is unlikely to inhibit CYP 2D6 or CYP 3A4[48]. Thus, we can hypothesize that hypericum might affect P450 enzymes other than CYP 2D6 and 3A4.

Symptoms of central serotonin excess (serotonin syndrome) have been reported in five patients who were receiving hypericum in combination with a stable dose of an SSRI[49]. Hence, combinations of SJW with other antidepressants or other serotonergic agents (e.g. antimigraine agents) cannot be recommended until further safety data become available. Caution should also be used when switching to SJW from an SSRI or MAOI or from SJW to an SSRI or MAOI and an appropriate washout may be prudent[50].

SJW has been reported to cause prolongation of narcotic-induced sleeping time and to antagonize the effects of reserpine. It may cause a reduction in barbiturate-induced sleeping times. Phototoxicity may be increased by the presence of photosensitizing drugs such as chlorpromazine or tetracycline. In a study conducted by Johne *et al.*, after the achievement of steady state of digoxin on day 5, 25 healthy volunteers received digoxin (0.25%) either with

placebo or 900 mg day^{-1} of LI 160 for 10 days. Hypericum was found to decrease the levels of digoxin and this interaction was found to be time dependent. The mechanism involved may be induction of P-glycoprotein drug transporter[51]. Hypericum effects have been found to be antagonized by drugs that reduce dopamine activity, e.g. haloperidol, sulpride, methyltyrosine.

Herbal drug interactions should be interpreted in light of the fact that most prescription antidepressants also have a varying degree of potential for drug interactions. In addition, the actual risk for a significant interaction can vary based on multiple factors such as dose, plasma level, genetic enzyme variability, concomitant medications and inherent tolerability. Hence, the clinical significance of most of the above interactions is not yet established.

Long-term controlled trials in clinically relevant populations are needed to establish the safety profile of SJW in relation to placebo and prescription antidepressants. Pending such data no safety recommendations can be made with certainty, and it is important for physicians to counsel patients appropriately.

Conclusion

Considering the pre-clinical and clinical data published to date, we cannot make any definitive conclusions about how SJW compares with prescription antidepressants and psychotherapy. However, SJW is the best researched herbal remedy for MDD and the data are highly promising. A multicentre placebo controlled trial sponsored by the National Institute of Health is currently underway to evaluate the safety and efficacy of a standardized extract of SJW (LI-160). SJW will be dosed initially at 900 mg daily with the option to titrate up to 1800 mg daily based on clinical response. A third arm consisting of sertraline (Zoloft, dosed from 50 to 150 mg daily) is included to ensure the validity of the trial. A total of 336 patients with DSM-IV diagnosed MDD, with a minimum score of 20 on the HAMD will be included. The trial has an acute treatment phase that will last for 8 weeks and then responders will have an option of continuing on blinded therapy for an additional 16 weeks. Further information on this study can be obtained at the hypericum web site: http://hypericum.rti.org/index.html.

In addition, there are three other trials of SJW underway in the US for MDD and another major clinical trial in Australia evaluating the efficacy of hypericum in comparison with SSRI. There are also studies underway in Europe examining the efficacy of SJW in anxiety disorders and in premenstrual disorders. It is hoped that results of the ongoing studies will help clarify the efficacy of SJW as a treatment of major depression and whether such efficacy is maintained. Additional studies are needed to test SJW in other subtypes of depression such as geriatric depression, childhood depression, dysthymia and bipolar depression. Further research is also warranted to test the comparative tolerability and safety of SJW in medically ill patients, during pregnancy and lactation as well as in combination with other prescription drugs. At present, pending such data, it is important for health care practitioners to counsel and educate patients about depression and the effectiveness of prescription antidepressants as well as psychotherapies, at the same time remaining open minded as to the emerging findings on SJW.

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