St. John's Wort

Hypericum perforatum L.

[Fam. *Clusiaceae*]

Overview

In the fifth century B.C.E., the Greek physician Hippocrates was one of the first to document therapeutic uses of St. John's wort (SJW). It rose from virtual obscurity in the U.S. to become the fifth best-selling dietary supplement in mainstream retail stores in the U.S. after major media coverage of clinical research documenting its relative safety and efficacy for treating mild to moderate depression. The National Institutes of Health's (NIH) National Center for Complementary and Alternative Medicine (NCCAM) recently sponsored a three-year, multi-center trial comparing the effects of a standardized extract of SJW and the selective serotonin reuptake inhibitor (SSRI), sertraline (Zoloft®). Since 1979, there have been more than 35 controlled clinical studies of SJW extracts for the treatment of mild to moderate depression. Several meta-analyses have documented the relative safety and probable efficacy of this phytomedicine. SJW is prescribed frequently by healthcare providers in Germany, where approximately 130 million preparations containing SJW were prescribed in 1999.

Primary Uses

Internal

- Depression, mild to moderate

External

- Healing wounds (acute and contused injuries)
- First-degree burns
- Myalgia (muscle pain)

Other Potential Uses

- Seasonal Affective Disorder (SAD)
- Obsessive-Compulsive Disorder (OCD)
- Menopause
- Fatigue
- Pediatric nocturnal incontinence
- Premenstrual Syndrome (PMS)

Pharmacological Actions

Antidepressant, relaxant, improves mental performance, does not change alertness or have sedative effect; may have relaxing effect and improve concentration, memory, and receptivity.

Dosage and Administration

For depression, the onset of response to SJW is similar to that for conventional antidepressants, requiring 2–4 weeks, or as long as 6 weeks. To prevent relapse, antidepressant should be continued at full therapeutic doses for at least 6 months after remission.

Internal

Crude Preparations

FLUID EXTRACT: 1:1 (*g/ml*), 2 ml, twice daily.

Standardized Preparations

DRY EXTRACT: 5–7:1, 300 mg, 3 times daily.

EXTRACT: Standardized to 0.3% hypericin, 900 mg daily in 3 divided doses; standardized to 2–4.5% hyperforin, 900 mg daily in 3 divided doses.

External

OILY MACERATE (OLEUM HYPERICI): Fresh-flowering tops in olive oil or wheatgerm oil are macerated for several weeks, stirred often, strained through a cloth and the pulp pressed. To be applied directly to affected areas.

Contraindications

None known, according to the German Commission E (1984, 1990 revision)

PREGNANCY AND LACTATION: No known restrictions.

Adverse Effects

In general, SJW produces few adverse side effects. Between October 1991 and December 1999, over 8 million patients are estimated to have been treated with Germany's leading SJW preparation with only 95 reports of side effects. These included "allergic" skin reactions (27), increased Quick Values (prothrombin time) (16), gastrointestinal complaints (9), breakthrough bleeding (birth control pill) (8), plasma cyclosporin reductions (7), and others. Photosensitization, depicted by erythema (redness of the skin) with exposure to sunlight or other ultraviolet radiation, is possible, but relatively rare and is sometimes reported in fair-skinned individuals taking excessive dosages (1,800 mg/day). A recent review of SJW adverse reactions suggests this precaution should not constitute a general contraindication, since photosensitization is so rare and because sunlight can promote recovery from depression.

Drug Interactions

Potential drug interactions with SJW have become the primary area of concern with this popular phytomedicine. However, some of these concerns may not be supported by clinical experience. In a review of drug interactions reportedly associated with SJW, calculations show one interaction per 300,000 treatments with the leading German SJW product.

SJW should not be taken in combination with any pharmaceutical antidepressants without professional guidance. SJW is believed to interact with oral contraceptives and anticoagulants (e.g., warfarin). Preliminary findings suggest that SJW does not

interact with the effects of alcohol; however, patients with depression should avoid alcohol. An uncontrolled study on 13 subjects taking SJW at normal doses (900 mg standardized extract/day) resulted in significant increases in urinary 6–beta–hydroxycortisol/cortisol ratio, suggesting that SJW is an inducer of CYP3A4, since cortisol is metabolized primarily by CYP3A4. A recent study revealed that constituents of SJW extract, especially hyperforin, are potent ligands (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with SJW extracts, or hyperforin, results in a marked induction of CYP3A4 expression. CYP3A4 is involved in the oxidative metabolism of more than 50% of all drugs and can cause a decrease in the therapeutic activity and concentration of such drugs, including contraceptives and theophylline. SJW also may increase clearance from the bloodstream of the protease inhibitor Indinavir, and the anti-rejection drug cyclosporine and may also interfere with the absorption of digoxin. A recent study found that SJW induces intestinal P-glycoprotein/MDR1 (in rats and humans), and induces intestinal and hepatic CYP3A4 (in humans), thereby decreasing plasma levels of cyclosporine, Indinavir, and digoxin. However, a review of SJW drug interactions questions the clinical relevance of interactions based solely on pharmacokinetic measurements, with digoxin, theophylline, and amitriptyline needing to be examined critically, since reduced plasma levels are not the same as reduced active levels at the receptors. To-date there are no reported cases suggesting clinically significant weakening in effect of the three drugs cited. One 14-day study on 10 patients, using the anti-seizure drug carbamazepine (Tegretol®), found that 300 mg SJW extract, three times daily, did not increase the clearance of the drug. Sudden discontinuation of SJW after prolonged use may lead to higher plasma levels of these drugs if used simultaneously, with the risk of adverse effects.

Clinical Review

Of 23 studies outlined in the table of clinical studies on SJW (2,745 total participants), all but two studies demonstrate positive effects of SJW on depression. Five randomized, double-blind, placebo-controlled (R, DB, PC) studies (626 participants) concluded that SJW significantly benefits patients with depression without significant side effects. Five R, DB, multicenter (MC) trials (1,191 participants) found equal effectiveness to tricyclic antidepressant drugs (amitriptyline, imipramine, malprotiline) with greater tolerability, and that SJW was safer for the heart.

Three small pilot studies (60 total patients) show promising findings for fatigue and SAD, and one small open-label study (12 patients) indicated potential benefits for OCD. One small pilot study of SJW for the treatment of premenstrual syndrome suggests that SJW might reduce the severity and duration of premenstrual symptoms, warranting a larger R, DB trial. A drug-monitoring study on menopausal symptoms suggests that SJW is useful for treatment of associated symptoms and increasing the sense of sexuality in middle-age women.

In a review of 17 studies on SJW and 9 studies on fluoxetine (Prozac®), researchers showed that SJW was as effective as fluoxetine in the treatment of subthreshold and mild depression. Researchers concluded that SJW may be a viable approach to avoiding the risk that mild depression becomes a full-blown disorder.

A review and meta-analysis of 23 clinical studies on SJW showed that the standardized extract was more effective than placebo in treating mild to moderate depression. A follow-up meta-analysis (27 trials; 2,291 patients) concluded that SJW was significantly superior to placebo and that short term use of SJW might be valuable in less severe forms of depression as an alternative to watchful waiting or low doses of tricyclic antidepressants with fewer short term adverse side effects. A recent trial comparing SJW with the conventional antidepressant imipramine is the largest comparison trial to date and the first to compare the two agents at the normal daily dose of imipramine (150 mg). (Previous trials used 75 mg imipramine to reduce adverse side effects and maintain patient compliance.) This study concluded that SJW is equivalent to imipramine in efficacy, and is better-tolerated by patients. A newer, larger trial (n=240) comparing SJW directly with fluoxetine concluded that SJW was equivalent to fluoxetine in efficacy, particularly in depressive patients suffering from anxiety, and was better tolerated for safety. A total of 11 studies have compared SJW preparations with conventional antidepressants (7 tricyclic; 4 SSRI) concluding that SJW is effective for mild to moderate depression with a low side effect profile.

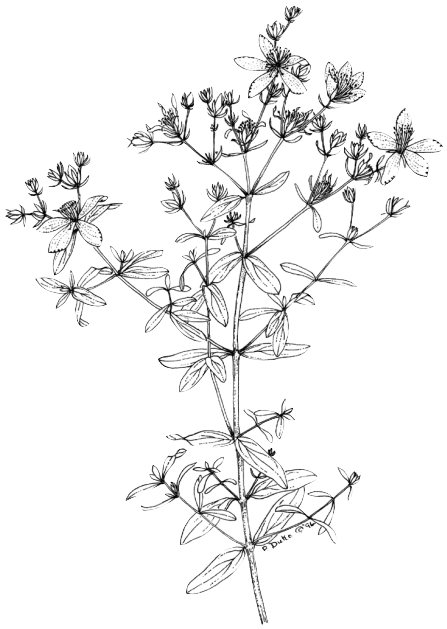
A recently published systematic review of 8 well-controlled R, DB, controlled (C), trials suggested that SJW is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with SJW ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. Treatment with SJW and fluoxetine was compared in patients with mild to moderate depression. Results showed that SJW and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although SJW may be superior in improving the responder rate, the main difference between the two treatments is safety. SJW was superior to fluoxetine in overall incidence of side effects, number of patients with side effects, and the types of side effects reported. A previous review of 15 C clinical trials (12 PC) reported that the only substantial documentation for the use of SJW in mild to moderate depression is for the products Jarsin® 300 (Lichtwer Pharma) and Psychotonin-M® (Steigerwald). The review concluded that SJW should not be taken for more than 6 weeks, since most trials showing efficacy have been conducted over a shorter period of time. A recent study received considerable media attention due to its negative findings on patients with severe depression; however, the study lacked an active control (no active drug was used to measure the response rate of severely depressed patients vs. SJW and placebo). The first study funded by the NIH's NCCAM (R, DB, PC, MC, 340 participants) found that neither sertraline nor SJW were effective compared to placebo for moderately severe major depressive disorder. Critics emphasize that the initial design included patients with major depression of only mild to moderate severity (HAMD score $\geq$ 15) but was later changed to include patients with moderate to severe depression (HAMD score $\geq$ 20).

St. John's wort

Hypericum perforatum
[Fam. *Clusiaceae*]

Overview

St. John's wort (SJW) rose from virtual obscurity in the U.S. to become the fifth best-selling dietary supplement in mainstream retail stores. Its rise to fame came after the national media reported clinical research showing that SJW is safe and effective for treating mild to moderate depression. The Greek physician Hippocrates (ca. 460-377 B.C.E.) was one of the first to speak of the health benefits of SJW. Preparations include teas, alcoholic tinctures, and tablets using either the plant in its crude form or standardized preparation. SJW is typically standardized to contain a consistent level of hypericin (0.3%), or hyperforin (3-5%), two naturally occurring chemicals found in the plant.



Uses

Internal

Depression (mild to moderate).

External

Wound healing; first-degree burns; muscle pain (myalgia).

Other Potential Uses

Seasonal Affective Disorder (SAD: mental depression related to certain seasons, especially winter); obsessive-compulsive disorder (OCD); menopause; fatigue; pediatric nocturnal incontinence; premenstral syndrome (PMS).

Dosage

FLUID EXTRACT: 1:1 (*g/ml*), 2 ml, twice daily.

DRY EXTRACT: 5–7:1, 300 mg, 3 times daily.

EXTRACT (STANDARDIZED): standardized to 0.3% hypericin or 2–4.5% hyperforin; 900 mg daily in 3 divided doses.

Contraindications

No known contraindications.

PREGNANCY AND LACTATION: No known restrictions.

Adverse Effects

Photosensitization (redness of the skin caused by exposure to sunlight or other ultraviolet radiation), especially in fair-skinned individuals, may occur with excessive dosages (1,800 mg/day), but this reaction is relatively rare.

Drug Interactions

SJW should not be taken in combination with any pharmaceutical antidepressants unless under professional guidance. SJW may interact with oral contraceptives, anticoagulant drugs like warfarin, the asthma drug theophylline, the anti-HIV drug Indinavir, the immunosuppressant drug cyclosporine, and the cardiac medication digoxin. Abruptly stopping SJW after prolonged use may increase the concentration of drugs like carbamazepine (Tegretol®). Patients with depression should avoid alcohol. Because SJW has been shown to potentially act with these and possibly other drugs, consumers and patients are advised to consult with a properly qualified healthcare professional before using SJW with any other over-the-counter or prescription medications.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

St. John's Wort

Hypericum perforatum L.

[Fam. *Clusiaceae*]

Overview

St. John's wort (SJW) has been used for various ailments since the ancient Greeks; the Greek physician Hippocrates (ca.400 B.C.E.) was one of the first to document its therapeutic use. Since the time of the Swiss physician Paracelsus (ca. 1540 C.E.) it was used to treat mental disorders (Blumenthal *et al.,* 2000; Hobbs, 1988/89). SJW rose from virtual obscurity in the U.S. to become the fifth best-selling dietary supplement in mainstream retail stores in 2000 (Blumenthal, 2001) following major media coverage of clinical research documenting its relative safety and efficacy for treating mild to moderate depression. In 1998 and 1999 it had risen to second place in mainstream sales (Brevoort, 1998), but fell to fifth place due, in part, to some adverse publicity regarding reports of its interactions with several classes of prescription drugs (Blumenthal, 2001). The

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National Institutes of Health's (NIH) National Center for Complementary and Alternative Medicine (NCCAM) recently sponsored a three-year, multi-center trial comparing the effects of a standardized extract of SJW and the selective serotonin reuptake inhibitor (SSRI) sertraline (Hypericum Depression Trial Study Group, 2002). Since 1979, there have been more than 35 controlled clinical studies of SJW extracts for the treatment of mild to moderate depression (Blumenthal *et al.*, 2000). Two meta-analyses have documented the relative safety and suggested probable efficacy of this phytomedicine (Linde and Mulrow, 2001; Linde *et al.*, 1996). SJW is prescribed frequently by healthcare providers in Germany, where approximately 130 million daily doses containing hypericum were prescribed in 1999 (Schulz, 2001). SJW preparations have also been used in traditional European herbal medicine for topical antimicrobial and skin healing purposes (Reichling *et al.*, 2001).

Description

St. John's wort (*Hypericum perforatum* L., Fam. *Clusiaceae*) preparations consist of dried above-ground parts (flowers and stems), gathered during the flowering season. Preparations include aqueous extracts (teas), standardized extracts, alcoholic tinctures, dry extracts in capsules or tablets, and oil infusions (topical) (Blumenthal *et al.,* 2000). Standardization is typically to 0.3% hypericin, or 2–4.5% hyperforin (Bruneton, 1999). *In vitro* research suggests that hyperforin may be the main antidepressive constituent (Muller *et al.*, 1998). However, flavonoids and other fractions have also shown antidepressant activity, suggesting "additive or synergistic actions of different single compounds may be responsible for the antidepressant efficacy of SJW" (Butterweck *et al.*, 2002b). The *German Drug Codex* formerly required that SJW preparations be standardized to hypericins content; this is no longer a required chemical marker (Bühler, 1995). The U.S. *National Formulary* requires not less than 0.04% total hypericins, calculated as hypericin (USP, 2002).

Primary Uses

Internal

Depression

- Mild to moderate (Harrer *et al.*, 1994; Harrer and Sommer, 1994; Laakmann *et al.*, 1998a; Lenoir *et al.*, 1999; Linde *et al.*, 1996; Linde and Mulrow, 2001; Philipp *et al.*, 1999; Wheatley, 1997; WHO, 2002; Woelk, 2000)

External

- Healing wounds (acute and contused injuries) according to the German Commission E (Blumenthal *et al.*, 1998)
- First-degree burns (Blumenthal *et al.*, 1998)
- Relieving myalgia (muscle pain) (Blumenthal *et al.*, 1998)

Other Potential Uses

(Based mainly on pilot studies)

- Seasonal Affective Disorder (SAD) (Kasper, 1997; Martinez *et al.*, 1994)
- Obsessive-Compulsive Disorder (OCD) (Taylor and Kobak, 2000)
- Premenstrual syndrome (Stevinson and Ernst, 2000)
- Menopause (Grube *et al.*, 1999)
- Fatigue (according to a pilot study) (Stevinson *et al.*, 1998)
- Pediatric nocturnal incontinence (clinical experience) (Weiss and Fintelmann, 2000)

Dosage

Internal

Crude Preparations

FLUID EXTRACT: 1:1 (*g/ml*), 2 ml, twice daily.

DRY EXTRACT: 5–7:1, 300 mg, 3 times daily (Blumenthal *et al.*, 2000).

Standardized Preparations

EXTRACT: Standardized to 0.3% hypericin, 900 mg daily in 3 doses of 300 mg each; or products standardized to 2–4.5% hyperforin, 900 mg/day in 3 doses (Bruneton, 1999).

External

OILY MACERATE (OLEUM HYPERICI): Fresh-flowering tops in olive oil or wheatgerm oil are macerated for several weeks, stirred often, strained through a cloth and the pulp pressed. To be applied directly to affected areas (Blumenthal *et al.*, 2000).

DURATION OF ADMINISTRATION

For depression, the onset of response to SJW is similar to that for conventional antidepressants, requiring 2–4 weeks, or as long as 6 weeks. To prevent relapse, antidepressant should be continued at full therapeutic doses for at least 6 months after remission (AHCPR, 1999).

CHEMISTRY

SJW contains 6.5–15% catechin-type tannins and condensed-type proanthocyanidins (catechin, epicatechin, leucocyanidin); 2–5% flavonoids, mostly 0.5–2% hyperoside, 0.3–1.6% rutin, 0.3% quercitrin, 0.3% isoquercitrin, quercetin, and kaempferol; bioflavonoids (about 0.26% biapigenin), phloroglucinol derivatives (up to 4% hyperforin); phenolic acids (caffeic, chlorogenic, ferulic); 0.05–1.0% volatile oils, mainly higher n-alkanes, 0.05–0.15% naphthodianthrones (hypericin and pseudohypericin); sterols (sitosterol); vitamins C and A, up to 10 ppm xanthones; and choline (Bruneton, 1999; ESCOP, 1996; Leung and Foster, 1996; Newall *et al.*, 1996; Upton, 1997; Wichtl and Bisset, 1994).

PHARMACOLOGICAL ACTIONS

Standardized Preparations

Human

The primary action of SJW is antidepressant (Phillipp *et al.*, 1999; Lenoir *et al.*, 1999; Leakmann *et al.*, 1998a, 1998b; Wheatley, 1997; Linde *et al.*, 1996). Some references refer to relaxant effects in relation to the Commission E approval for anxiety and nervous unrest, but this may only be in the context of the overall antidepressant activity (Schulz *et al.*, 2000) or in small studies on sleep continuity (Schulz *et al.*, 1995) or resting EEG (Johnson *et al.*, 1994). Other actions include improved mental performance possibly resulting from improvement of depressed states (Lehrl *et al.*, 1993). SJW does not appear to change alertness or have sedative effects; there may be some additional central nervous system effects, again related to improvement of depression including improvement of concentration, memory, and receptivity (Schulz *et al.*, 2000; Schulz *et al.*, 1994; Johnson *et al.*, 1994; Lehrl, 1993).

Animal

Many animal studies have been published on SJW demonstrating a variety of actions, including the following, suggesting antidepressant activity: SJW potentiates dopaminergic behavioral responses (alcoholic extracts), and serotoninergic effects (carbon dioxide extracts) (Bhattacharya, 1998); reduces alcohol intake in rats (Rezvani *et al.*, 1999); SJW extract and hypericin given daily for 8 weeks significantly increased 5-HT (serotonin) levels in rat hypothalamus (Butterweck *et al.*, 2002a); and flavonoids from SJW showed antidepressant activity in rats in the forced swimming test (Butterweck *et al.*, 2000).

In vitro

There has been confusion about the potential monoamine oxidase (MAO) inhibiting effect of SJW. Earlier research suggested that SJW possibly inhibits MAO, using 80% pure hypericin (Suzuki *et al.*, 1984). However, a more recent study suggests that 95% pure hypericin does not inhibit MAO, but a crude ethanolic extract (Herb Pharm, Williams, OR) does, at 2 mcg/ml (Cott, 1995). MAOI activity has *not* been reported *in vivo* in animals or in humans (Cott, 1997). SJW unspecifically inhibits biogenic amine and amino acid neurotransmitter uptake (serotonin, dopamine, noradrenaline, GABA, L-glutamate) (Chatterjee *et al.,* 1998; Butterweck *et al.*, 1997); inhibits serotonin reuptake (Perovic and Müller, 1995; Müller and Rossol, 1994; Holzl, 1989); is antiretroviral (using purified hypericin) (Lavie *et al.*, 1990; Meruelo *et al.*, 1988); modulates interleukin-1x (hypericin) (Panossian *et al.*, 1996) and interleukin-6 (SJW) (Thiele *et al.*, 1994); is antiviral (influenza and herpes simplex type 1) (Serkedjieva *et al.,* 1990), and is antimicrobial (primarily hyperforin) toward methicillin-resistant *Staphylococcus aureus* but not against gram-negative bacteria or *Candida albicans* (Reichling *et al.*, 2001). Isolated hypericin from SJW extracts showed highest phototoxicity *in vitro*, but this was controlled by the flavonoid fraction, particularly quercitrin (Wilhelm *et al.*, 2001).

MECHANISM OF ACTION

- Components of a hydro-ethanolic SJW extract bound with high affinity at $GABA_A$, $GABA_B$, adenosine, benzodiazepine, inositol, triphosphate, and MAO-A and MAO-B receptors (Cott, 1997).
- May inhibit uptake of several neurotransmitters (Müller and Rossol, 1994; Perovic and Müller, 1995; Holzl, 1989; Chatterjee *et al.*, 1998; Raffa, 1998; Butterweck *et al.*, 1997).
- May inhibit uptake of neuropeptides and neurosteroids (Perovic and Müller, 1995; Holzl *et al.*, 1989; Chatterjee *et al.*, 1998; Raffa, 1998; Butterweck *et al.*, 1997).
- SJW may inhibit 5-hydroxytryptamine (5HT, serotonin) receptor expression resulting in inhibition of 5HT reuptake (Müller and Rossol, 1994).
- One indirect study based on changes in hormone levels suggests that antidepressant effects might be mediated mainly through changes in serotonin and dopamine neurotransmission but not noradrenaline (in humans) (Franklin and Cowen, 2001).
- May act on information substances (shared components of immune and nervous systems) such as leukotriene B4 and interleukin-1a inhibiting release of arachidonic acid, leukotriene B4, production of IL–1α, and activating NO synthesis (Panossian *et al.*, 1996; Thiele *et al.*, 1994).
- Hyperforin, but not hypericin, in SJW induces CYP3A4 expression in human hepatocytes and activates the steroid X receptor, possibly suggesting a mechanism for drug interactions (Moore *et al.,* 2000; Wentworth *et al.,* 2000).
- Hyperforin from SJW leads to elevation of Na^+, thus explaining its apparent effect on serotonin uptake inhibition into platelets and synaptosomes and the non-selective profile on many neurotransmitter transport systems which are driven by Na^+ gradient membranes (Müller *et al.*, 2001).

Contraindications

The Commission E stated "none known" in 1984 and in the 1990 monograph revision (Blumenthal *et al.*, 1998). Recent drug interaction reports suggest professional guidance when certain conventional pharmaceuticals may be simultaneously administered (see Drug Interactions).

Pregnancy and Lactation: No known restrictions. Animal reproductive studies did not produce mutagenicity at relatively high doses (Upton *et al.*, 1997). Due to lack of available data, the WHO monograph recommends that SJW not be administered during pregnancy or nursing without advice of a healthcare provider (WHO, 2002).

Adverse Effects

In general, SJW produces few adverse side effects. Between October 1991 and December 1999, over 8 million patients are estimated to have been treated with Germany's leading SJW preparation (Jarsin® or Jarsin®300); during this period only 95 reports of side effects were received by the German Adverse Drug Reaction Recording System. These included "allergic" skin reactions (27 reports), increased Quick Values (prothrombin time) (16), gastrointestinal complaints (9), breakthrough bleeding (birth control pill) (8), plasma cyclosporin reductions (7), and others (Schulz, 2001). Photosensitization, depicted by erythema (redness of the skin) with exposure to sunlight or other ultraviolet radiation is possible, although this is relatively rare and is sometimes reported in fair-skinned individuals taking excessive dosages (1,800 mg/day) (Brockmuller, 1997; Blumenthal *et al.,* 1998). A recent review of SJW adverse reactions suggests that this precaution should not constitute a general contraindication, since the incidence of photosensitization is so rare and because sunlight can promote recovery from depression (Schulz, 2001).

Drug Interactions

Potential drug interactions with SJW have become the primary area of concern with this popular phytomedicine. However, one source suggests that some of these concerns may not be borne out by clinical experience. In a review of drug interactions reportedly associate with SJW, the author calculates one interaction per 300,000 treatments with the leading German SJW product (Jarsin®, Schulz, 2001).

SJW should not be taken in combination with any pharmaceutical antidepressants (Gordon, 1998; Prost *et al.,* 2000), unless under professional guidance. SJW is believed to interact with oral contraceptives and anticoagulants (e.g., warfarin) (TGA, 2000; Di Carlo *et al.*, 2001; Lantz *et al.*, 1999; McGuffin *et al.*, 1997). Preliminary findings suggest that SJW does not interact with the effects of alcohol; however, patients with depression should avoid alcohol (Schmidt, 1993). An uncontrolled study on 13 subjects taking SJW at normal doses (900 mg of the standardized extract/day), resulted in significant increases in urinary 6–beta–hydroxycortisol/cortisol ratio, suggesting that SJW is an inducer of CYP3A4, since cortisol is metabolized primarily by CYP3A4 (Roby *et al.*, 2000). A recent study (Moore, 2000) revealed that constituents of SJW extract, especially hyperforin, are a potent ligand (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with SJW extracts, or hyperforin, results in a marked induction of CYP3A4 expression. CYP3A4 is involved in the oxidative metabolism of more than 50% of all drugs, and can cause a decrease in the therapeutic activity and concentration of such drugs, including contraceptives (Moore, 2000) and possibly theophylline (Baede-van Dijk *et al.*, 2000). SJW also may increase clearance from the bloodstream of the protease inhibitor indinavir, and the anti-rejection drug cyclosporine (Piscitelli *et al.*, 2000; Ruschitzka *et al.*, 2000), and may also interfere with the absorption of digoxin (Tatro, 2000). A recent study found that SJW induces intestinal P-glycoprotein/MDR1 (in rats and humans), and induces intestinal and hepatic CYP3A4 (in humans), thereby decreasing plasma levels of cyclosporine, indinavir, and digoxin (Dürr *et al.*, 2000). However, a review of SJW drug interactions questions the clinical relevance of interactions that are postulated solely on the basis of pharmacokinetic measurements, with digoxin, theophylline, and amitriptyline needing to be examined critically, since reduced plasma levels are not the same as reduced active levels at the receptors. The author states that to-date there are no reported cases suggestive of a clinically significant weakening in effect of the three drugs cited (Schulz, 2001). One 14-day study on 10 patients, using the antiseizure drug carbamazepine (Tegretol®), found that 300 mg St. John's wort extract, three times daily, did not increase the clearance of the drug (Burstein *et al.*, 2000). Sudden discontinuation of SJW after prolonged use may lead to higher plasma levels of these drugs if used simultaneously, with the risk of adverse effects (Baede-van Dijk *et al.*, 2000).

American Herbal Products Association (AHPA) Safety Rating

Class 2d: Based on earlier *in vitro* research and the Commission E monograph, AHPA cautioned that SJW may potentiate pharmaceutical MAO-inhibitors (McGuffin *et al.*, 1997), although there are no animal or human data to support this.

Regulatory Status

Australia: Complementary medicine available without prescription from pharmacies, health food shops, supermarkets, and complementary medicine practitioners (TGA, 2000). Required label warning: "St. John's wort affects the way some prescription medicines work. Consult your doctor." (Trickey, 2000).

Canada: Nonprescription drug for internal or external use classified as either "Schedule OTC Herbs and Natural Products" or "Schedule Homeopathic Products," in either case requiring premarketing authorization and assignment of Drug Identification Number (DIN) by the Therapeutic Products Programme (TPP) (Health Canada, 2001a). In January 2001, added to "Drugs of Current Interest (DOCI) List" maintained by the Canadian Adverse Drug Reaction Monitoring Program (Health Canada, 2001b). Potential drug-interaction warning statement required.

European Union: Whole or cut, dried, flowering tops harvested during flowering time, containing no less than 0.08% total hypericins, official in the *European Pharmacopoeia* (Ph.Eur., 2001).

France: Dried flowering top or aerial part official in *French Pharmacopoeia* approved only for external use but not prior to sun exposure (Bruneton, 1999; ESCOP, 1996).

Germany: Approved by Commission E as a nonprescription drug for internal and external use (Blumenthal *et al.*, 1998). Whole or cut aerial parts, collected just before or during the flowering period, official for internal or external use in the *German Drug Codex* supplement to the *German Pharmacopoeia* (DAC, 1998). Whole,

fresh, flowering plant for preparation of mother tincture is official in German Commission D monographs and corresponding *German Homeopathic Pharmacopoeia* (BAnz, 1985; GHP, 1993).

SWEDEN: Classified as Natural Remedy, requiring premarket authorization. As of January 2001, nine SJW-containing products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies," and a monograph is published with the approved indication: "Traditionally used in case of slight mood lowering and for minor nervous tension" (MPA, 1999; 2001a; Tunón, 1999). St. John's wort homeopathic preparations are also registered drugs (MPA, 2001b).

SWITZERLAND: Official in *Swiss Pharmacopoeia* (Upton *et al.*, 1997; Wichtl, 1997). Herbal medicine with positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; Ruppanner and Schaefer, 2000). Numerous SJW phytomedicines and homeopathic preparations are listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2000).

U.K.: Licensed product for internal use; *General Sale List* (GSL), Table B (external use only), Schedule 1 (requires full product license) (GSL, 1994). A recent article reviewed the benefits and risks of SJW and their regulatory implications in the U.K. (McIntyre, 2000).

U.S.: Dietary supplement (USC, 1994). Dried, flowering tops gathered shortly before or during flowering, containing no less than 0.04% total hypericins, official in U.S. *National Formulary*, 19th edition (USP, 2002).

Clinical Review

Twenty-three studies are outlined in the following table, "Clinical Studies on St. John's Wort", including a total of 2,745 participants. All but three of these studies (Lenoir *et al.*, 1999; Shelton *et al.,* 2001; Hypericum Depression Trial Study Group, 2002) demonstrate positive effects of SJW on depression. Five randomized, double-blind, placebo-controlled (R, DB, PC) studies have been performed on 626 participants, concluding that SJW significantly benefits patients with depression without significant side effects (Philipp *et al.*, 1999; Laakmann *et al.*, 1998a, 1998b; Harrer and Sommer 1994; Hübner *et al.*, 1994; Hänsgen *et al.*, 1994). Five R, DB multicenter (MC) trials, with 1,191 participants, found equal effectiveness to tricyclic antidepressant drugs (amitriptyline, imipramine, malprotiline) with greater tolerability for SJW (Wheatley, 1997; Vorbach *et al.*, 1994; Harrer *et al.,* 1994), and that SJW was safer for the heart than tricyclic antidepressants (Czekalla *et al.*, 1997).

Three small pilot studies on a total of 60 patients show promising findings for the conditions of fatigue and SAD (Stevinson *et al.,* 1998; Kasper, 1997; Matinez *et al.*, 1994), and one small open-label (OL) study on 12 patients indicated the potential benefits of SJW for OCD (Taylor and Kobak, 2000). One small pilot study of SJW for the treatment of PMS suggests that SJW might improve the severity and duration of premenstrual symptoms, warranting a larger R, DB trial (Stevinson and Ernst, 2000). A drug-monitoring study on menopausal symptoms suggests that SJW is useful for treatment of associated symptoms, and increasing the sense of sexuality in middle-age women (Grube *et al.*, 1999).

In a review of 17 studies on SJW and 9 studies on fluoxetine (Prozac®), researchers showed that SJW was as effective as fluoxetine in the treatment of subthreshold and mild depression (Volz, 2000). Researchers concluded that SJW is effective in subthreshold depression exhibiting very few or no side effects, easy availability, and may be a viable approach to avoiding the risk that mild depression becomes a full-blown disorder.

A review and meta-analysis of 23 clinical studies on SJW showed that the extract was more effective than placebo in treating mild to moderate depression (Linde *et al.*, 1996). Based on the evidence available at the time, the same review concluded that further studies were needed to establish whether SJW is as effective as conventional antidepressant drugs (Linde *et al.*, 1996). A follow-up meta-analysis by the Cochrane Center of 27 trials with 2,291 patients concluded that SJW was significantly superior to placebo (Linde and Mulrow, 2001). The review concluded that the short term use of SJW might be valuable in less severe forms of depression as an alternative to watchful waiting or the commonly used approach to low doses of tricyclic antidepressants and that SJW has less short term adverse side effects than tricyclics. A recent trial comparing SJW with the conventional antidepressant imipramine is the first to compare the two agents at the normal daily dose of imipramine (150 mg) (Woelk, 2000). Previous trials used only 75 mg imipramine in order to reduce adverse side effects and maintain patient compliance. This study is the largest comparison trial to date and concluded that the SJW extract used in the study (Remotiv® marketed by Bayer in Germany) is equivalent to imipramine in efficacy, and is more well-tolerated by patients. A newer, larger trial (n=240) comparing SJW (Ze 117) directly with fluoxetine concluded that SJW was of equivalent efficacy as fluoxetine, particularly in depressive patients suffering from anxiety, and was better tolerated for safety than the SSRI (Friede *et al.*, 2001). A total of 11 studies have compared SJW preparations with conventional antidepressants (7 tricyclic; 4 SSRI) concluding that SJW is effective for mild to moderate depression with a low side effect profile (Kasper, 2001).

A recently published systematic review of R, C, DB trials selected, and assessed for methodological quality, eight well-controlled studies (Gaster and Holroyd, 2000). The results suggest that SJW is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of SJW ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. The treatment with SJW and the commonly used SSRI fluoxetine (Prozac®), was compared in patients with mild to moderate depression. The results showed that SJW and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although SJW may be superior in improving the responder rate, the main difference between the two treatments is safety. SJW was superior to fluoxetine in overall incidence of side effects, number of patients with side effects, and the type of side effect reported (Schrader, 2000). A previous review of 15 controlled clinical trials (12 PC) reported that the only substantial documentation for the use of SJW in mild to moderate depression is for the products Jarsin® 300 (Lichtwer Pharma) and Psychotonin-M® (Steigerwald) (Volz, 1997). The review concluded that SJW should not be taken for more than 6 weeks, since most trials showing efficacy have been conducted over a shorter period of time. A recent study by Shelton *et al.* (2001) received considerable media attention due to its negative findings on patients with severe depression. The study was noted for its lack of an active control (no SSRI or other active drug was used to measure the response rate of severely depressed patients vs. SJW and placebo) (Cott *et al.*, 2001).

Results were recently published for the first study funded by the NIH's NCCAM. This long awaited and much publicized R, DB, PC, MC, 3-arm study (340 participants) found that neither sertraline (Zoloft®) nor SJW were effective compared to placebo for moderately severe major depressive disorder. Critics emphasize that the initial design included patients with major depression of only mild to moderate severity (HAMD score ≥ 15) but was later changed to include patients with moderate to severe depression (HAMD score ≥ 20). Widespread publicity on this trial focused on the failure of SJW without equally noting the failure of sertraline which was given a slight edge over SJW because of sertraline's better performance on a secondary measure (a Clinical Global Impression scale that included partial responders). (Outcomes on secondary measurements are not considered appropriate measures for ascribing success or failure.) The authors of this study acknowledged that 35% of clinical trials on known antidepressant drugs failed. More than 50% of trials with investigational antidepressant drugs fail (Robinson and Rickels, 2000).

Branded Products*

Hyperiforce®: Bioforce AG / CH-9325 Roggwil TG / Switzerland / Tel: +41 71 454 61 61 / Fax: +41 71 454 61 62 / www.bioforce.com / Email: info@bioforce.ch. 275 mg/tablet of a 1:9.0 ethanol/water extract of fresh tips of shoots. One tablet 3 times/day after meals provides 1 mg hypericin/day.

Jarsin® 300: Lichtwer Pharma AG / Wallenroder Strasse 8-14 / 13435 Berlin / Germany / Tel: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. 300 mg St. John's wort extract/capsule in coated tablets standardized to 0.3% total hypericins.

Kira®: Lichtwer Pharma AG, c/o ABKIT, INC. / 207 East 94th Street / New York, NY 10128 / U.S.A. / Tel: 800-226-6227 / Fax: 212-860-8323 / www.abkit.com / Email: info@abkit.com. 300 mg dried methanolic extract produced from leaves, stems, and flowers standardized to 300 mcg total hypericin.

LI 160: Lichtwer Pharma AG. 300 mg St. John's wort extract/capsule in coated tablets standardized to 0.3% total hypericins.

Remotiv®: Bayer Vital GmbH & Co. KG / Consumer Care / Welser Strasse 5 – 7 / 51149 Köln / Germany / Tel: + 49-01-30-82-6301 / www.bayer-ag.de. Each 250 mg film-coated tablet of St. John's wort extracted in 50% alcohol, standardized to 2% hypericins.

STEI 300: Steiner Arzneimittel / Postfach 450520 / 12175 Berlin / Germany / Tel: +49-03-07-1094-0 / Fax: +49-03-07-1250-12 / www.steinerarznei-berlin.de. Each 350 mg capsule contains 0.2%–0.3% hypericin, and 2%–3% hyperforin.

WS 5570: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4 / D-76227, Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / Email: melville-eaves@schwabe.de / www.schwabepharma.com. An 80% *v/v* hydroalcoholic extract of St. John's wort, drug to extract ratio 3–7.1.

WS 5572: Dr. Willmar Schwabe Pharmaceuticals. St. John's wort extract standardized to 5% hyperforin.

WS 5573: Dr. Wilmar Schwabe Phramaceuticals. Each 300 mg capsule contains dry SJW extract standardized to 0.5% hyperforin.

Ze 117: Zeller AG / Seeblickstrasse 4 / CH-8590 Romanshorn 1 / Switzerland / www.zellerag.ch. St. John's wort extracted in 50% alcohol, standardized to 2% hypericins in a 250 mg tablet, drug to extract ratio 4–7:1.

*American equivalents are found in the Product Table beginning on page 398.

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Clinical Studies on St. John's wort (*Hypericum perforatum* L.)

Depression

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Hypericum Depression Trial Study Group, 2002	Major depression	R, DB, PC, MC n=340 adults with baseline total HAMD score ≥ 20	8–18 weeks	900–1,500 mg SJW/day or 50–100 mg sertraline/day or placebo; divided into 3 doses/day	LI 160 SJW extract standardized to between 0.12% and 0.28% hypericin; sertraline (Zoloft®)	Initial treatment phase = 8 weeks. Patients responding positively were given respective treatments for additional 18 weeks. On the 2 primary outcome measures neither sertraline nor SJW performed significantly differently from placebo, based on HAMD or CGI scale. Full response occurred in 31.9% placebo group, 24.8% sertraline group (p=0.26), and 23.9% SJW group (p=0.21). Sertraline was better than placebo on a secondary measure: a CGI improvement scale that included partial responders (p=0.02). Authors concluded that the study does not support the efficacy of SJW in moderately severe major depression, acknowledging the low assay sensitivity of this trial, and the fact that 35% of trials on known antidepressants result in failure.
Friede *et al.*, 2001	Mild to moderate depression	R, DB, MC n=240 (HAMD scores 16–24)	6 weeks	500 mg/day Ze 117 vs. 20 mg/day fluoxetine	Ze 117 vs. fluoxetine	SJW extract is equivalent in efficacy (p=0.09) to fluoxetine for both overall depressive symptoms and the main symptoms of depressive disorders. SJW is particularly effective in depressive patients suffering from anxiety symptoms. Tolerability for SJW revealed better safety (p<0.001) than for fluoxetine.
Shelton *et al.*, 2001	Severe depression	R, DB, PC, MC n=200 patients with baseline HAMD ≥ 20	SJW for 4 weeks (n=98) or placebo (n=102) for 8 weeks	900 mg/day increased to 1200 mg/day or placebo	SJW standardized extract (LI 160) or placebo	The number of patients with a remission of depression was significantly higher with SJW than placebo (p=0.2), but they had low rates 14.3% with SJW vs. 4.9% for placebo in the full intention-to-treat analysis. SJW was well tolerated, with the only adverse effect being headaches (41% vs. 25%). The random analyses for the HAMD, HAMA, CGI-S, and CGI-I showed significant effects for time but not for treatment or time-by-treatment interaction. The study concluded that SJW was not effective in treating major depression (no active control used).
Brenner *et al.*, 2000	Mild to moderate depression; comparison of SJW and selective serotonin reuptake inhibitors (SSRIs)	R, DB, C n=30	7 weeks	600 mg per day of standardized SJW extract or 50 mg per day of sertraline for 1 week, followed by 900 mg per day of SJW or 75 mg per day of sertraline	LI 160 vs. sertraline	Severity of symptoms, as measured by HAMD and the Clinical Gobal Impression scale was significantly reduced in both treatment groups (p<0.01). The difference in clinical response, based on reduction in HAMD for each group, was not statistically significant. SJW extract was found to be at least as effective as sertraline in treating mild to moderate depression.
Woelk, 2000	Mild to moderate depression without suicidal ideation (ICD-10)	R, DB, PG, MC (40 centers) n=324 HAMD scale >18. Mean HAMD 22.4 (SJW); 22.1 (imipramine) (ages >18 years)	6 weeks	250 mg SJW extract, 2x/day; 75 mg imipramine, 2x/day	Remotiv® (Ze 117) vs. imipramine	157 subjects on SJW had HAMD scores drop from mean or 22.4 at baseline to 12.00 at 12 weeks end, compared to 167 imipramine patients' scores of 22.1 dropping to 12.75 (no statistical difference between groups). CGI scores at end were mean of 2.22 of 7 for SJW group and 2.42 for imipramine group (no statistical difference between groups). In self-assessment, mean scores were 2.44 for SJW and 2.60 for imipramine (no statistical difference between groups). Tolerability scores were better for SJW (1.65) than drug (2.35); (no statistical difference between groups). Researchers concluded that SJW is therapeutically equal to imipramine for mild to moderate depression and tolerated better. This is largest trial on SJW comparing it to imipramine at standard dose (150 mg/day).
Philipp *et al.*, 1999	Moderate depression	R, DB, MC, PG, PC, Cm n=262	2 months	1050 mg/day SJW , 350 mg, 3x/day vs. daily dosing of 50 mg, 25 mg, then 25 mg (100 mg total/day) imipramine	STEI 300 vs. imipramine	SJW was more effective than placebo and as effective as 100 mg/day imipramine in the treatment of depression as measured by HAMD, HAMA, and Clinical Global Impression scales. Improved quality of life also demonstrated in Zung self-rating depression scale. Proven safe with less adverse effects than imipramine.

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Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Depression (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Lenoir *et al*., 1999	Mild to moderate depression (ICD-10)	R, DB, PG, Cm, MC n =260 (over 20 years old)	6 weeks	1 tablet 3x/day (1 mg total hypericin/day or 33 mg total hypericin/day or 17 mg total hypericin/day)	Hyperiforce® tablets containing approximately 60 mg SJW extract (4–5:1) of shoot tips standardized to 0.33 mg total hypericin content/tablet (controls standardized to 0.11 mg or 0.055 mg total hypericin/ tablet)	At the end of the treatment period, a reduction of about 50% in Hamilton Depression scores was observed in all groups. No significant differences between dosages. SJW was determined to be effective in all 3 doses and is well tolerated.
Laakmann *et al*., 1998a	Mild to moderate depression	R, DB, PC, MC, PG n=145 (mean age, 51 years placebo; 48.7 years W5573 group; 47.3 years SJW group)	7 weeks	900 mg/day (300 mg, 3x/day)	WS 5573 (0.5% hyperforin) or WS 5572 (5% hyperforin) or placebo	Study demonstrated relationship between hyperforin dose and antidepressant efficacy. 5% hyperforin SJW product enhanced patients' quality of life by producing appreciable relief from symptoms compared to 0.5% (p=0.017) and placebo (p=0.004). No statistical difference between 0.5% and placebo. Study suggests hyperforin is a therapeutically active constituent with antidepressant activity.
Wheatley, 1997	Mild to moderate depression (DSM-IV)	R, DB, PG, MC n=156 (HAMD score between 17–24, mean score SJW=20.6 amitriptylline= 20.8) (ages 20–65 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) or amitriptyline (3x25 mg in a fixed dose manner)	LI 160 vs. amitriptyline	Comparable efficacy to amitriptyline with clear tolerability advantage. No statistically significant difference in response rate was shown between SJW and amitriptyline (p=0.064). In the CGI item "side-effects of drugs," greater tolerability for SJW was apparent (p<0.001 at week 2, p<0.05 at weeks 4 and 6).
Schrader *et al*., 1998	Mild to moderate depression	R, P, DB, PC, MC n=159	6 weeks	One, 250 mg tablets SJW extract 2x daily (1 mg hypericin daily)	Ze 117 SJW extract standardized to 0.5 mg hypericin/ tablet	Of SJW patients, 56% were deemed responsive to treatment compared to 15% on placebo. There were few adverse effects: 5 placebo, 6 SJW (mostly minor gastrointestinal upsets in SJW group). Researchers noted that the good tolerability profile contributed to the high compliance of the SJW group.
Vorbach *et al*., 1994	Typical depression with single episode, recurrent episode, neurotic depression, and adjustment disorder with depressed mood (DSM-III-R).	R, DB, Cm, MC n=130 (mean HAMD score: 20.2 SJW group; 19.4 imipramine group) (ages 18–75 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) vs. imipramine (3x25mg daily)	LI 160 vs. imipramine	SJW showed equal effectiveness to and better tolerability than imipramine. Improved HAMD total score by 56% on SJW and 45% on imipramine. SJW caused less frequent and less severe side effects than imipramine.
Harrer *et al*., 1994	Depression (ICD-10)	R, DB, Cm, MC n=102 (HAMD score >16) (ages 25–65 years)	4 weeks	900 mg/day SJW extract (300 mg, 3x/day), maprotiline, (25 mg 3x/day)	LI 160 vs. maprotiline	Showed roughly equal efficacy to maprotiline. No significant difference between groups on HAMD, D-S, and CGI scores (HAMD score >16). 25% in SJW group and 35% in maprotiline group reported adverse drug effects.

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Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Depression (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Harrer and Sommer, 1994	Mild to moderate depression (ICD-9)	R, DB, PC, MC n=89 (HAMD score <20) (ages 20–64 years)	1 month	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly (p<0.05) reduced depressive symptoms after 2 weeks and even further after 4 weeks (p<0.01) compared to placebo. No notable side effects were reported.
Hübner *et al*., 1994	Mild depression and somatic symptoms (ICD-09)	R, DB, PC n=39 (Mean HAMD score 12.55 SJW group, 12.37 placebo group) (ages 20–64 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significant reduction in HAMD score in SJW group compared to placebo (p<0.01). Final score=7.17. Significant reduction in falling asleep compared to placebo (p<0.01). Benefited patients with good tolerability and high compliance (p<0.05). By week 4, 5% statistical difference level in HAMD between placebo and SJW groups. No adverse effects reported.
Hänsgen *et al*., 1994	Major depression and temporary depressive neurosis (DSM-III-R)	R, DB, PC, MC n=72 (HAMD score >16) (ages 18–70 years)	6 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly improved all 4 psychometric tests vs. placebo, with no serious side effects reported: Hamilton depression scale (p<0.001), depression scale of von Zerssen (p<0.001), complaint inventory, Clinical Global Impression Scale.

Fatigue and Seasonal Affective Disorder

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Stevinson *et al*., 1998	Fatigue	O, U, pilot n=20 (mean age, 44.4 years)	6 weeks	900 mcg/day hypericin (300 mcg 3x/day)	Kira®	Significantly lowered perceived fatigue after 2 weeks (p<0.05) and reduced significantly more after 6 weeks (p<0.01). Significantly (p<0.05) reduced mean scores of depression and anxiety.
Martinez *et al*., 1994	Seasonal affective disorder (SAD) (DSM-III-R) HAMD scale>16	R, SB n=20 (ages 29–63 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 with bright light (3000 lux) vs. LI 160 with dim light (<300 lux)	Significant improvement in symptoms over time with SJW and bright light (p=0.001). No adverse drug reactions reported.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Shüle *et al*, 2001	Effect of SJW on cortisol, growth hormone, and prolactin	R, PC, CO n=12 healthy males between 20 and 35 years old	5 hours	300 mg WS 5570, 600 mg WS 5570, or placebo	WS 5570 SJW extract or placebo	No prolactin stimulation was observed (p>0.05) in SJW or placebo. A small but statistically significant (p<0.05) increase in growth hormone occurred after 300 mg SJW. After 600 mg SJW, cortisol stimulation was clearly observed (p<0.05) from 30 to 90 minutes after application.
Schempp *et al*., 2001	Phototoxicity of SJW in treatment of depression (UV-B, UV-A, visible light, solar-simulated radiation)	R, P n=72	Single-dose or steady-state 7 days	Single dose: 6 or 12 coated tablets, 3x daily (containing 5400 or 10,800 mcg total hypericins). Steady-state trial: initial dose of 6 tablets (1800 mcg hypericins) followed by 3 x 1 tablets (2700 mcg) per day for 7 days	LI 160	No significant changes were observed (erythema and melanin index) in either the single or multiple doses administered, with the exception of a slight, (p=0.50) influence on UV-B-induced pigmentation. The authors concluded that this study did not indicate phototoxic potential in the oral administration of higher than therapeutic doses (2–4 times) of SJW for depression.

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Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Other (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Burnstein *et al*., 2000	SJW effects on steady state carbamazepine and carbamazepine-10,11-epoxide pharmacokinetics	U n=8	21 days	100 mg 2x/day for 3 days, then 200 mg, 2x/day for 3 days, then 400 mg 1x/day for 14 days; then 300 mg SJW with carbamazepine, 3x/day for 14 days	St. John's wort (0.3% standardized tablet) or carbamazepine (brand not stated)	The study concluded that SJW did not increase clearance of carbamazepine.
Taylor and Kobak, 2000	Obsessive-compulsive disorder (OCD)	O n=12 patients with 12 months diagnosis of OCD (DSM-IV)	12 weeks	450 mg SJW extract, 2x/day	450 mg SJW extract standardized to 0.3% hypericin (brand not stated)	Significant change from baseline, with mean change in Yale-Brown Obsessive-Compulsive Scale of 7.4 points (p=0.01). At end of trial, 5 patients were rated much or very much improved on clinician CGI, 6 were minimally improved, and 1 had no change. Side effects included diarrhea (3 subjects) and restless sleep (2 subjects). Improvements noted in first week. Results warrant placebo-controlled study of SJW for OCD.
Grube *et al*., 1999	Menopausal symptoms	O Drug monitoring study n=106 women 43–65 years old with symptoms characteristic of pre- and post-menopause	12 weeks	One, 300 mg tablet, 3x/day	Kira®	Self-assessment by Menopause Rating Scale for assessing sexuality and CGI. Psychological, psychosomatic, and vasomotor symptoms recorded at baseline, 5, 8, and 12 weeks. Significant improvement in psychological and psychosomatic symptoms. Menopausal symptoms reduced or disappeared in majority (76.4% by patient assessment; 79.2% by physician assessment). About 80% of women considered sexuality was improved with SJW
Czekalla *et al*., 1997	Electrocardiogram effects in patients with depression	R, DB, Cm, MC n=209	6 weeks	1,800 mg/day or 150 mg/ day imipramine	Jarsin® 300 vs. imipramine	SJW did not delay conduction through the atria or depolarization and repolarization in the ventricles. Imipramine increased heart rate and can cause pathological repolarization. High-dose SJW extract (i.e., 2x normal daily dose) produced fewer cardiac conduction defects than tricyclic antidepressants for treating elderly patients or patients with a pre-existing conductive dysfunction, and should be considered safer than tricyclic antidepressants, especially in patients with pre-existing conduction disorders.

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