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Medical Attributes of St. John's Wort (Hypericum perforatum)

Kenneth M. Klemow, Andrew Bartlow, Justin Crawford, Neil Kocher, Jay Shah, and Michael Ritsick.

11.1 INTRODUCTION

St. John's wort (SJW), known botanically as Hypericum perforatum, is a sprawling, leafy herb that grows in open, disturbed areas throughout much of the world's temperate regions. The use of this species as an herbal remedy to treat a variety of internal and external ailments dates back to the time of the ancient Greeks. Since then, it has remained a popular treatment for anxiety, depression, cuts, and burns. Recent research suggests the effectiveness of this herb in treating other ailments, including cancer, inflammation-related disorders, and bacterial and viral diseases, and as an antioxidant and neuroprotective agent. Pharmaceutical companies, particularly in Europe, prepare standard formulations of this herb that are taken by millions of people. Worldwide annual sales of products made from SJW presently exceed several billion dollars. Further, SJW produces dozens of biologically active substances, although two—hypericin (a naphthodianthrone) and hyperforin (a lipophilic phloroglucinol)—have the greatest medical activity. Other compounds, including the flavonoids rutin, quercetin, and kaempferol, also appear to have medical activity. H. perforatum has been intensively studied on isolated tissue samples, using animal models and through human clinical trials. The effectiveness of SJW as an antidepression agent is particularly well studied, and the underlying mechanisms are well understood. SJW preparations have relatively few adverse effects when taken alone at the recommended dosages. However, numerous interactions with other drugs have been reported. Recent research shows these interactions result from the ability of SJW constituents to induce intestinal or hepatic enzymes that either remove drugs from the body or metabolize them to inactive forms. This chapter examines the constituents, modes of action, and adverse interactions of SJW, providing an up-to-date synthesis of a large body of literature that has developed over the past 30 years regarding this widely taken herbal remedy. Some recommendations regarding future research needs are also presented.

11.2 TAXONOMY AND DESCRIPTION

Commonly called SJW, klamath weed, tipton weed, goat weed, and enola weed (Muenscher 1946), H. perforatum is a perennial flowering herb belonging to the Clusiaceae (Mangosteen family; alternatively, Hypericaceae and Guttiferae). The genus Hypericum consists of

approximately 400 species of herbs and shrubs having yellow or coppery flowers with four to five petals, numerous stamens, and a single pistil (Gleason and Cronquist 1991).

H. perforatum consist of freely branching shrubby herbs that typically range from 40 to 80 cm in height (Muenscher 1946; Gleason and Cronquist 1991). The stems and branches are densely covered by oblong, smooth-margined leaves that range from 1 to 3 cm long and 0.3-1.0 cm wide (Figure 11.1). The leaves are interrupted by minute translucent spots that are evident when held up to the light. The upper portions of mature plants can produce several dozen five-petaled yellow flowers that are typically 1.0-2.0 cm wide. The edges of the petals are usually covered with black dots. Crushed flowers produce a blood-red pigment. By late summer, the flowers produce capsules that contain dozens of tiny, dark-brown seeds. The species is a native of Europe, but has spread to temperate locations in Asia, Africa, Australia, and North and South America (Gleason and Cronquist 1991; Foster 2000). It thrives in poor soils, and is commonly found in meadows, fields, waste areas, roadsides, and abandoned mines and quarries (Muenscher 1946; Klemow and Raynal 1983; Gleason and Cronquist 1991). Due to concerns over phototoxicity to livestock, H. perforatum is listed as a noxious weed in seven western states in the United States. Programs promoting its eradication are underway in Canada, California, and Australia.

FIGURE 11.1. Diagrams of St.

Diagrams of St. John's wort (Hypericumperforatum). A sketch of the lower stem showing leaf arrangement is to the left, and that of the upper stem with flowers is to the right. An opened capsule is shown in the bottom left, and a flower petal is (more...)

11.3 TRADITIONAL ORIGINS

The SJW has been considered a medicinally valuable plant for over 2000 years. The Greek physicians of the first century, Galen, Dioscorides, Pliny, and Hippocrates, recommended SJW as a diuretic, wound-healing herb, treatment for menstrual disorders, and cure for intestinal worms and snakebites (Foster 2000; Castleman 2001; Redvers et al. 2001). Dried flowering tops placed in olive oil caused the oil to turn red after 3 weeks. The ancients believed the plant had mystical qualities, and plants were collected for protection from demons and to drive away evil spirits. In fact, the generic name Hypericum originated from the Greek name for the plant, hyperikon. Literally translated, the name is an amalgamation of the root words "hyper" (meaning over) and "eikon" (meaning image or apparition), referring to the plant's supposed ability to ward off evil spirits (Foster 2000). Early Christians also believed the plant had mystical properties. According to one legend, the greatest effect was obtained when the plant was harvested on Saint John's Day (June 24), which is often the time of peak blooming (Foster 2000). Another legend holds that the plant released its blood-red oil on August 29, the day of St. John's beheading (Castleman 2001).

The plant enjoyed continued use as an herbal remedy in the Middle Ages. Sixteenth-century herbalists including Paracelsus, Gerard, and Culpeper all recommended SJW preparations to treat wounds and alleviate pain (Foster 2000; Castleman 2001). In 1525, Paracelsus recommended it for treating depression, melancholy, and overexcitation (Clement et al. 2006). The SJW's use as a medicinal herb continued in Europe, spreading to other continents, between the eighteenth and nineteenth centuries. It was commonly made into teas and tinctures for treatment of anxiety, depression, insomnia, water retention, and gastritis. Over the years, vegetable oil preparations have been used for treatment of hemorrhoids and inflammation. Others have used SJW extracts to treat sores, cuts, minor burns, and abrasions, especially those involving nerve damage (Blumenthal et al. 1998; Foster 2000; Foster and Duke 2000; Castleman 2001).

11.4 CURRENT USAGE AND PREPARATIONS

SJW is currently valued for treating depression and other mood disorders. Products containing SJW in the form of tablets, capsules, teas, and tinctures accounted for an estimated US$6 billion in Europe in the late 1990s (Ernst 1999; Greeson, Sanford, and Monti 2001). In the United States, annual sales reached a peak of US$315 million in 1998, but declined to approximately US$60 million by 2006 (Tilburt, Emanuel, and Miller 2008). SJW has been the subject of several pharmacopoeias and monographs, including the British Herbal Pharmacopoeia (1996), the European Scientific Cooperative on Phytotherapy (ESCOP 1996), the American Herbal Pharmacopeia (1997), and the European Pharmacopoeia (European Directorate for the Quality of Medicines (EDQM) 2000), among others (Parfitt 1999; Barnes, Anderson, and Phillipson 2001).

Several pharmaceutical-grade preparations of SJW are commercially available, typically extracted from dried aerial parts. The LI 160, produced by Lichtwer Pharma, is standardized to contain 0.3% hypericin derivatives, and normally comes in 300-mg capsules (Bloomfield, Nordfors, and McWilliams 1996). Another product, Ze 117, produced by Zeller AG, Switzerland, is a 50% ethanolic extract with an herb-to-extract ratio of between 4:1 and 7:1. The hyperforin content of Ze 117 is 0.2%, lower than that of LI 160, whose hyperforin

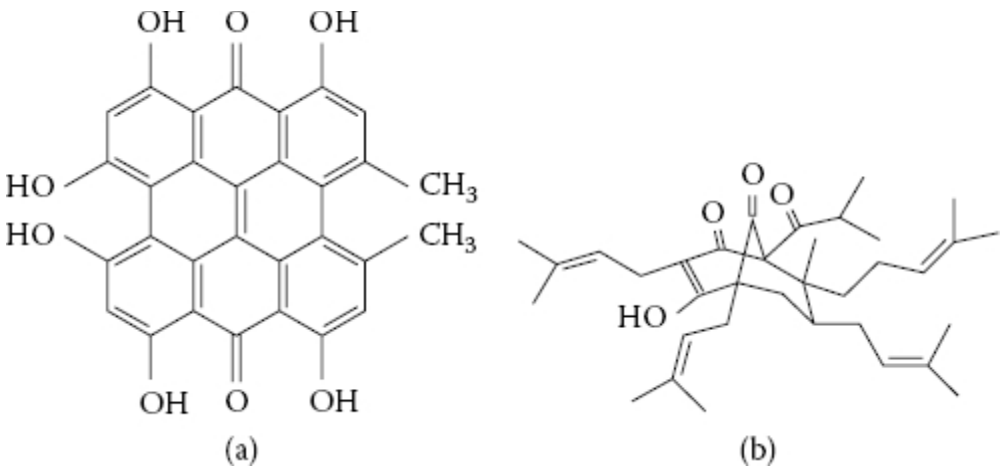
content ranges between 1% and 4%. The dosage of Ze 117 is 500 mg/day (Marquez 2002). The product WS 5570, produced by Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany, is an 80% ethanolic extract of SJW with a plant-to-extract ratio of between 3:1 and 3:1-7:1 (Barrett 2004). It contains 5-6% hyperforin and 0.12-0.28% hypericin (Lecrubier et al. 2002; Szegedi et al. 2005). Tablets contain 300 or 600 mg of extract. The product WS 5572 has similar hyperforin and hypericin profile to WS 5570, but has a plant-to-extract ratio of between 2.5:1 and 5:1 (Barrett 2004). The product STEI 300, produced by Steiner Arzneimittel of Berlin, contains 0.2-0.3% hypericin and pseudohypericin, and 2-3% hyperforin (Philipp, Kohnen, and Hiller 1999). Capsules contain 350 mg of extract. The German Commission E and European Scientific Cooperative on Phytotherapy (ESCOP) monographs recommend 900 mg of standardized extract per day (ESCOP 1996; Blumenthal et al. 1998). Clinical trials using various H. perforatum preparations allow typical dosages in the range of 300-1800 mg/day (Barnes, Anderson, and Phillipson 2001).

In the United States, SJW, like all herbal remedies, is listed as a dietary supplement by the Food and Drug Administration (FDA). Therefore, it is not subject to the strict scrutiny for safety and efficacy that standard pharmaceutical drugs are required to pass (Clement et al. 2006). The FDA mandates that all herbal remedies contain a disclaimer informing the consumer that any claims about the medicine's therapeutic value have not been evaluated by that agency.

11.5 ACTIVE INGREDIENTS

Chemical investigations into the constituents of H. perforatum have detected seven groups of medicinally active compounds (Nahrstedt and Butterwick 1997). The most common classes include naphthodianthrones, phloroglucinols, and flavonoids (such as phenylpropanes, flavonol glycosides, and biflavones), as well as essential oils (Bombardelli and Morazzoni 1995; Reuter 1998; Barnes, Anderson, and Phillipson 2001; DerMarderosian and Beutler 2002). Two major active constituents have been identified: hypericin (a naphtodianthrone; Figure 11.2a) and hyperforin (a phloroglucinol; Figure 11.2b). However, roughly 20% of extractable compounds are considered biologically active (Staffeldt et al. 1994; Nahrstedt and Butterwick 1997; Erdelmeier 1998).

FIGURE 11.2. Chemical structures of (a) hypericin, and (b) hyperforin.



(a) (b)

Chemical structures of (a) hypericin, and (b) hyperforin.

11.5.1 Naphthodianthrones

The class of compounds isolated from H. perforatum that is the most researched is the naphthodianthrones, which have been standardized in concentrations ranging from 0.1% to 0.3% (Robbers and Tyler 1999; Grainger-Bisset and Wichtl 2001; Greeson, Sanford, and Monti 2001). The most common naphthodianthrones include hypericin, pseudohypericin, isophypericin, and protohypericin (Barnes, Anderson, and Phillipson 2001; DerMarderosian and Beutler 2002). Of these, hypericin—an anthraquinone-derived pigment that is responsible for the red color of SJW oils—is the best known. Hypericin is found in the flowers, particularly in the black dots that are located along the petals.

Due to its chemical structure, hypericin is highly photoreactive. Biochemically, hypericin is a polycyclic quinone, possessing four hydroxyl groups that are positioned adjacent to two carbonyl groups (Figure 11.2a). Owing to resonance of the molecule and the relatively short distance between oxygen atoms (approximately 2.5 Å), the hydroxyl hydrogen is capable of transferring between the hydroxyl oxygen and the carbonyl oxygen in the presence of fluorescent light (Petrich 2000). The hydrogen is therefore in constant flux between the two oxygen atoms when exposed to fluorescent light (Smirnov and Fulton 1999). Studies examining the fluorescence spectrum of hypericin and its analogs demonstrate the existence of a "protonated" carbonyl group, supporting the H-atom transition mechanism (Petrich 2000). This hydrogen transfer also causes acidification of the surrounding environment (Fehr, McCloskey, and Petrich 1995; Sureau et al. 1996).

11.5.2 Flavonoids

Flavonoids found in SJW range from 7% in stems to 12% in flowers (DerMarderosian and Beutler 2002) and leaves (Greeson, Sanford, and Monti 2001). Flavonoids include flavonols (kaempferol, quercetin), flavones (luteolin), glycosides (hyperside, isoquercitrin, and rutin), biflavones (biapi-genin), amentoflavone, myricetin, hyperin, oligomeric proanthocyanadins, and miquelianin, all of which are biogenetically related (Reuter 1998; Barnes, Anderson, and Phillipson 2001). Rutin concentration is reported at 1.6% (Barnes, Anderson, and Phillipson 2001).

11.5.3 Lipophilic Compounds

Extracts of SJW contain several classes of lipophilic compounds with demonstrated therapeutic value, including phloroglucinol derivatives and oils. Hyperforin, isolated in concentrations of 2-4.5% (Chatterjee, Bhattacharya et al. 1998; Greeson, Sanford, and Monti 2001), is a prenylated phloroglucinol expanded into a bicyclo nonaendionol (2,1), substituted with several lipophilic isoprene chains (Nicolaou, Carenzi, and Jeso 2005). Hyperforin is unstable in the presence of both light and oxygen (Liu et al. 2005). Despite numerous attempts by various researchers, total synthesis of hyperforin has not been accomplished to date (Nicolaou, Carenzi, and Jeso 2005). Other phloroglucinols include adhyperforin (0.2%-1.9%), furohyperforin, and other hyperforin analogs (Hahn 1992; Barnes, Anderson, and Phillipson 2001; Greeson, Sanford, and Monti 2001; DerMarderosian and Beutler 2002).

Essential oils are found in concentrations ranging from 0.05% to 0.9% (Greeson, Sanford, and Monti 2001). They consist mainly of mono- and sesquiterpenes, specifically 2-methyl-octane, n-nonane, α- and β-pinene, α-terpineol, geranil, and trace amounts of myrecene, limonene, and caryophyllene, among others (Hahn 1992; Reuter 1998).

11.5.4 Additional Compounds

Other compounds of various classes have been identified in H. perforatum. These include tannins (ranging from 3% to 16%), xanthones (1.28 mg/100 g), phenolic compounds (caffeic acid, chlorogenic acid, and p-coumaric acid), and hyperfolin. Additional compounds include, to a lesser extent, acids (nicotinic, myristic, palmitic, and stearic), carotenoids, choline, pectin, hydrocarbons, and long-chain alcohols (DerMarderosian and Beutler 2002). Several amino acids that have been isolated from the herb include cysteine, glutamine, leucine, lysine, and GABA (γ-aminobutyric acid; Hahn 1992; Bombardelli and Morazzoni 1995; Greeson, Sanford, and Monti 2001).

11.6 HEALTH EFFECTS: THE SCIENTIFIC EVIDENCE

The widespread popularity of SJW's use as an herbal remedy results from studies that appear to verify its efficacy in treating a variety of diseases, especially depression. In turn, the herb's use has generated widespread interest among scientists seeking to firmly evaluate its effectiveness. Such studies include analyses on the effects of SJW extracts on isolated tissue samples, studies using animal models, and clinical analyses and meta-analyses of humans given SJW extracts.

11.6.1 St. John's Wort and Depression

Mood disorders are common illnesses that force individuals to seek relief offered by physicians and other health-care providers. All over the world, 3-5% of the population requires treatment for depression (Lieberman 1998). The disorder brings with it a series of symptoms such as strong feelings of sadness and guilt, a loss of interest or pleasure, irregular sleeping patterns, a loss of energy, decreased ability to concentrate, and an increase or decrease of appetite. Even more serious symptoms are repeated thoughts of suicide and death (Remick 2002).

Depression is thought to originate from a disruption of normal brain neurochemistry, specifically from a deficiency of amine neurotransmitters like acetylcholine, norepinephrine, dopamine, and serotonin (5-hydroxytryptamine [5-HT]). Antidepression drugs typically raise the levels of those neurotransmitters, especially in nerve-nerve synapses (Remick 2002).

Synthetic antidepressants available currently fall into two categories: (1) tricyclics and (2) selective serotonin reuptake inhibitors (SSRIs). Tricyclics include amitriptyline (brand name: Elavil), desipramine (Norpramin), imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), and trimipramine (Surmentil). Commonly prescribed SSRIs include citalopram (Celexa), fluoxetine

(Prozac), paroxetine (Paxil), and sertraline (Zoloft). Monoamine oxidase (MAO) inhibitors (MAOIs) like phenelzine (Nardil) and tranylcypromine (Parnate) are also used to treat depression (American Academy of Family Physicians 2000).

11.6.1.1 Active Principals: In Vitro Studies

Early research suggested that hypericin is the main antidepressant constituent of SJW, stimulating capillary blood flow (DerMarderosian and Beutler 2002). Later, studies on rat brain mitochondria found hypericin to strongly inhibit the enzymes MAO-A and -B (Suzuki et al. 1984; Robbers and Tyler 1999; Barnes, Anderson, and Phillipson 2001). MAO is involved in the degradation of amine neurotransmitters. Inhibiting their degradation boosts their levels in the synapse. However, further studies determined that hypericin's ability to inhibit MAO was lower than was originally estimated. Moreover, the levels of hypericin necessary to obtain significant MAO inhibition were far greater than those likely to be found in human brain tissue at normal doses (Suzuki et al. 1984; Chavez and Chavez 1997). Hypericin has been shown to have a strong affinity for sigma receptors, which regulate dopamine levels. It also acts as a receptor antagonist at adenosine, benzodiazepine, GABA-A, GABA-B, and inositol triphosphate receptors, which regulate action potentials caused by neurotransmitters (Chavez and Chavez 1997; Jellin et al. 2002). Although hypericin has been reported to have antidepressant properties, it cannot by itself completely account for the antidepressant activity of SJW. Recent research focuses on hyperforin as the antidepression agent (Cervo et al. 2002). Hyperforin is a potent reuptake inhibitor of serotonin, dopamine, noradrenaline, GABA, and L-glutamate from the synaptic cleft (Calapai et al. 1999; Vormfelde and Poser 2000; Müller, Singer, and Wonnemann 2001; Zanoli 2004). The IC50 values (concentration resulting in 50% inhibition) of approximately 0.05-0.1 µg/mL for neurotransmitters were reported in synaptosomal preparations (Chatterjee et al. 1998). Blocking the reuptake of serotonin (5-HT) from the synaptic cleft alleviates symptoms of depression by allowing the serotonin to bind to 5-HT receptors and elicit a greater response (Jones and Blackburn 2002; Molderings 2002).

Unlike synthetic antidepressants that block 5-HT receptors, hyperforin apparently inhibits serotonin uptake by elevating intracellular concentrations of sodium (Na) and calcium (Ca; Singer, Wonnemann, and Muller 1999; Müller, Singer, and Wonnemann 2001; Müller 2003). Treiber et al. (2005) demonstrated that the influx of Na+ was mediated by nonselective cation channels (NSCCs). They found that hyperforin acts on the subclass NSCC2, increasing intracellular concentrations of both Na+ and Ca2+ ions (Treiber et al. 2005). Leuner et al. (2007) subsequently identified the channel as being the transient receptor potential channel protein 6 (TRPC6). Thus, activation of TRPC6 by hyperforin leads to an increase in sodium uptake by neurons, resulting in a decrease of the sodium gradient between the neuron and the synaptic cleft. The loss of the gradient decreases reuptake of the monoamine neurotransmitters. The mechanism by which hyperforin has been shown to act is therefore different from that used by conventional antidepressants, perhaps pointing the way to a new class of antidepressants (Leuner et al. 2007). Hyperforin also increases the number of 5-HT receptors, as demonstrated by studies on rat brains (Teufel-Meyer and Gleitz 1997), suggesting a possible long-term therapeutic benefit of SJW treatment. Clinical trials also

demonstrated that the level of therapeutic effect of SJW extract is directly dependent on the concentration of hyperforin (Laakmann et al. 1998).

11.6.1.2 Clinical Studies

Since the 1980s, dozens of clinical studies have investigated the effectiveness of SJW. Some of the studies compared study populations receiving SJW to those receiving placebo. Others compared study populations receiving SJW to those receiving standard antidepressants. Other studies were three-armed, comparing study populations receiving SJW to a second study population receiving a standard antidepressant and a third receiving placebo.

Several meta-analyses of clinical studies have been conducted since the mid-1990s (Linde et al. 1996; Kim, Streltzer, and Goebert 1999; Linde and Mulrow 1998; Barnes, Anderson, and Phillipson 2001; Linde et al. 2005a, b; Clement et al. 2006; Linde, Berner, and Kriston 2009). Perhaps the most comprehensive—and widely recognized—meta-analyses are the Cochrane Reviews published by Linde and associates (Linde et al. 1996, 1998, 2005a; Linde, Berner, and Kriston 2009). These reviews were performed through computerized searches of several databases, based on published and unpublished trials conducted to that effect. Each review had specific inclusion criteria, with the criteria evolving over time. For example, to be included in their 1998 review, trials had to be randomized, include patients with depressive disorders, compare preparations that included SJW with placebos or other antidepressants, and include an objective clinical assessment of symptoms. Their analysis included 27 trials spanning a total of 2291 patients. Their 2005 review mandated that the trials be double-blind, administration of SJW with other plant extracts be avoided, trials have an SJW intervention of at least 4 weeks, and trials use only standard antidepressants (Linde et al. 2005b). A total of 37 trials, spanning 3405 patients, met their criteria. Conversely, in their 2009 review, trials were restricted to those including patients with major depression. A total of 29 trials with 5489 patients met those criteria.

Linde and Mulrow (1998) found that preparations containing H. perforatum extracts were significantly superior to placebo and as effective as standard antidepressants. Based on that evidence, the authors concluded that extracts of Hypericum are more effective than placebo for the short-term treatment of mild to moderately severe depressive disorders. However, they did not see sufficient evidence to establish whether SJW is as effective as other antidepressants.

Barnes, Anderson, and Phillipson (2001) reported on seven additional clinical studies examining monopreparations of SJW. In general, patients receiving SJW extracts reported a greater decrease in depression scores than those taking placebo and similar outcomes to those taking synthetic antidepressants.

Barnes, Anderson, and Phillipson (2001) noted that the trials comparing SJW to synthetic antidepressants were criticized because the dosages of the latter were unrealistically low.

Spira (2001) pointed to the study's usage of somewhat outdated tricyclics and the short (6 week) duration of the analysis.

In stark contrast to results of the mostly German studies conducted in the 1990s, two studies conducted in the United States concluded that SJW was ineffective in treating moderate to major depression. An assessment conducted in 11 academic medical centers in the United States. by Shelton et al. (2001) between 1998 and 2000 encompassed 200 adult outpatients who were diagnosed as having major depression. Their study found that remission rates were low: as much as 14.3% in the treatment versus 4.9% in the placebo control. Shelton et al. (2001) agreed that SJW was a safe and well-tolerated herb, with headache being the only adverse reaction that was higher in the herb group than in the placebo group. However, the authors concluded that SJW was not effective for treating major depression, and even questioned its efficacy for treating moderate depression.

A second study, conducted by the Hypericum Depression Trial Study Group (2002), was a double-blind multicenter investigation aimed at determining whether SJW (LI-160) was useful in treating major depression. The study involved 340 adult outpatients at 12 academic and community psychiatric research clinics in the United States. Their study had the benefit of being three-armed, involving comparisons against a control group receiving a placebo, and a second receiving the SSRI sertraline. The proportion of patients showing full or partial response to SJW was 47.6%, which was actually lower than those receiving placebo (55.9%) and sertraline (61.1%). Perhaps most note-worthy was the finding that statistically, response rates did not differ significantly between placebo and either SJW or sertraline. The authors concluded that the findings failed to support any claims of efficacy of H. perforatum in treating moderately severe depression. They admitted that their results might have been due to the low assay sensitivity of the trial. However, the three-armed design of the test was significant, because without a placebo group one might conclude that SJW was as effective as an established synthetic antidepressant.

The lack of statistical difference between Hypericum and placebo contrasted markedly with the findings of previous German studies that did find such a difference. Likewise, the lack of difference between sertraline and placebo was also striking. Rather than showing a lack of efficacy for either SJW or sertraline, Kupfer and Frank (2002) attributed the lack of statistical difference to an unusually high placebo response. They expressed concerns that variability in placebo response from trial to trial may obscure interpretation of controlled experiments on natural and synthetic antidepressants alike. Linde et al. (2002) speculated that the difference between U.S. and German studies may be due to the latter's focus on patients with mild to moderately severe depression. They suggest that studies may be needed to determine whether SJW appears to be particularly effective in Germany, and not elsewhere.

In their subsequent Cochrane Review that included studies up to May 2004, Linde et al. (2005a) observed that the effectiveness of SJW extracts depended on the size of and the setting in which the trial is located. Trials that were more likely to show a clear benefit of SJW over placebo were small (defined as below the median of the variance), excluded patients with major depression, were conducted in German-speaking countries (Germany, Switzerland, or Austria), and were published before 1995. Larger, more recent trials

restricted to patients having major depression and those conducted in the United States, the United Kingdom, France, and Sweden revealed only minor benefit of SJW over placebo. No difference between SJW and synthetic antidepressants—tricyclics or SSRIs—was noted. Compared to those receiving synthetics, patients receiving SJW reported fewer adverse effects and stayed in the trials at a higher rate. The latest Cochrane Review, limited to trials with individuals showing symptoms of major depression (Linde, Berner, and Kriston 2009), again showed heterogeneity for individuals given SJW compared to those given placebo. Nonetheless, the results showed a clear benefit to those receiving Hypericum. As noted in their previous Cochrane Reviews, the differential was more striking for smaller trials in German-speaking countries than for larger ones conducted in areas where German is not the prevailing language. No difference was observed between individuals given extracts of SJW and those given synthetic SSRIs. Linde, Berner, and Kriston (2009) reported few adverse effects of SJW administration, although they cautioned against the interactions of SJW with other prescribed drugs.

Studies reporting clinical trials published since the July 8, 2008 cutoff for the Linde, Berner and Kriston (2009) review also showed an advantage over placebo or similar benefits as observed for synthetic antidepressants (Kasper et al. 2008a,b; Brattström 2009; Rahimi, Nikfar, and Abdollahi 2009).

Thus, despite the negative findings of the Hypericum Depression Trial Study Group (2002), there is consensus among the research studies published to date that indicates the administration of H. perforatum is clearly helpful for treating mild to moderate depression. The findings of the most recent Cochrane Review (Linde, Berner, and Kriston 2009) also point to SJW's efficacy when the herb is given to patients experiencing major depression. Readers are cautioned, however, that the benefits are only applicable to standardized extracts of SJW such as LI 160, WS 5570/2, and ZE 117. All the recent clinical trials mentioned in the literature suggest that Hypericum is more tolerable than synthetic antidepressants as it causes fewer side effects and also shows similar adverse reactions as seen in placebo-controlled groups. This makes SJW an attractive option for treating depression.

11.6.2 Antibacterial and Antiviral Properties

As noted in Section 11.1, extracts of H. perforatum have been used over thousands of years to treat cuts, abrasions, and other wounds. Its usefulness in reducing inflammation is well known, and appears to be related, at least in part, to its ability to serve as an antibacterial agent. Recent research also suggests that it is useful in combating viruses.

Antibacterial properties of H. perforatum extracts were reported by Russian scientists in 1959 (Schempp et al. 1999). The main antibacterial component was determined to be hyperforin (Bystrov et al. 1975). Studies show that hyperforin inhibits the growth of certain types of microorganisms. Growth inhibition occurred for all gram-positive bacteria tested, although no growth-inhibitory effects were seen in the gram-negative bacteria tested (Bystrov et al. 1975). Methicillin-resistant (MRSA) and penicillin-resistant (PRSA) Staphylococcus aureus were especially susceptible to hyperforin. The MRSA strain was shown to be resistant to several types of penicillins, ofloxacin, clindamycin, erythromycin, cephalosporins, and gentamicin (Bystrov et al. 1975).

Extracts of SJW have long been regarded as being effective against various classes of viruses. Studies by Mishenkova et al. (1975) indicated that flavonoid and catechin-containing fractions of SJW are active against influenza virus. Since 1988, the virucidal activities of hypericin extract have been investigated against many other forms of viruses (Diwu 1995). Hypericin compounds are effective against enveloped viruses, but not nonenveloped viruses (Diwu 1995), particularly when activated by light (Carpenter and Kraus 1991; Hudson, Harris, and Towers 1993; Hudson, Graham, and Towers 1994). Hypericin inactivates enveloped viruses at different points in the viral life cycle (Lenard, Rabson, and Vanderoef 1993). Degar et al. (1992) suggested that hypericin inactivates enveloped viruses by altering viral proteins, and not nucleic acids as targeted by antiviral nucleosides. Hypericin also inhibits the ability of viruses to fuse with cell membranes (Degar et al. 1992; Lenard, Rabson, and Vanderoef 1993), which may explain why hypericin inactivates enveloped viruses rather than nonenveloped ones.

These promising in vitro results have begun to promote various in vivo studies of certain viruses in mice. These include LP-BMS murine immunodeficiency viruses, murine cytomegalovirus (MCMV), Sindbis virus, Friend virus, and Ranscher leukemia virus (Hudson, Lopez-Bazzocchi, and Towers 1991; Meruelo 1993; Stevenson and Lenard 1993). Hypericin also shows in vitro activity against influenza and herpes viruses (Tang et al. 1990), vesiculostomatitis and Sendai viruses (Lenard, Rabson, and Vanderoef 1993), and duck hepatitis B virus (Moraleda et al. 1993). Hypericin is used to inactivate several enveloped viruses present in human blood and to treat acquired immunodeficiency syndrome (AIDS) patients (Holden 1991; Meruelo 1993). Working with the human immunodeficiency virus (HIV), Degar et al. (1992) observed changes in the p24 protein and the p24-containing gag precursor, p55. They also observed that a recombinant p24 formed an anti-p24 immunoreactive material. This indicated the occurrence of alterations of p24, and such alterations may be able to inhibit the release of reverse transcriptase activity. In contrast, in a phase I clinical trial, Gulick et al. (1999) found that hypericin had no beneficial effect when administered to 30 HIV-infected patients with CD4 counts <350 cells/mm3. More recently, Maury et al. (2009) found that 3-hydroxy lauric acid in field-grown H. perforatum has anti-HIV activity. They assert that such anti-HIV activity can be developed into inexpensive therapies, expanding the current arsenal of antiretroviral agents.

Regarding other viruses, a noteworthy finding is that hypericin completely inactivated bovine diarrhea virus (BVDV) in vitro in the presence of light (Prince et al. 2000). Conversely, Jacobson et al. (2001) found that in the doses studied, hypericin demonstrated no effect on hepatitis C virus.

11.6.3 Anticancer Properties

Hyperforin and hypericin have also been examined for their anticancer properties. According to Schempp et al. (2002), hyperforin inhibits tumor cell growth in vitro. The mechanism involves induction of apoptosis (programmed cell death) through the activation of caspases, which are cysteine proteases that trigger a cascade of proteolytic cleavage occurrences in mammalian cells. Hyperforin also causes the release of cytochrome c from isolated mitochondria. Mitochondrial activation is an early event in hyperforin-mediated apoptosis,

and hyperforin inhibits tumor growth in vivo (Schempp et al. 2002). Schempp and his colleagues agreed that since hyperforin has significant antitumor activity, is readily available in high quantities (since it is naturally occurring in abundance), and has low toxicity in vivo, hyperforin holds promise of being an interesting novel antineoplastic agent. Other in vitro studies demonstrated that hyperforin in conjunction with polyphenolic procyanidin B2 effectively inhibited the growth of leukemia K562 and U937 cells, brain glioblastoma cells LN229, and normal human astrocytes (Hostanska et al. 2003).

Hypericin has also been investigated as an anticancer agent, reportedly inhibiting the growth of cells derived from a variety of neoplastic tissues, including glioma, neuroblastoma, adenoma, mesothelioma, melanoma, carcinoma, sarcoma, and leukemia (Fox et al. 1998). The activity of hypericin is attributed to its photodynamic properties (Agostinis et al. 2002). In the presence of light and oxygen, hypericin acts as a powerful natural photosensitizer, generating superoxide radicals that form peroxide or hydroxyl radicals, or singlet oxygen molecules that kill tumor cells. In this way, hypericin can be used as a component of photodynamic therapy (PDT; Agostinis et al. 2002). At first, PDT was used only for skin lesions, but it is becoming increasingly accepted as a treatment for many types of tumors.

Fox et al. (1998) found that hypericin photoactivated with white light or ultraviolet light or both could induce nearly complete apoptosis (94%) in malignant cutaneous T cells and lymphoma T cells. Similarly, Olivo, Du, and Bay (2006) suggested its applicability in treating nasopharyngeal cancer. In vitro studies have found that hypericin works synergistically with the anticancer agent 5-aminolevulinic acid (5-ALA) to stop formation of human esophageal cancer cells (Höpfner et al. 2003), and human endometrial cancer cells (HEC-1A; Schneider-Yin et al. 2009) when exposed to white light. Hypericin and 5-ALA work synergistically to induce protoporphyrin IX (PpIX), which, after conversion to porphyrin, converts oxygen to more reactive species that kill cancer cells (Schneider-Yin et al. 2009). Exposing tumors cells to hypericin in conjunction with laser irradiation led to toxic effects on human prostatic cancer cell lines (Colasanti et al. 2000), human urinary bladder carcinoma cells (Kamuhabwa et al. 2000), and pancreatic cancer cell lines (Liu et al. 2000) in in vitro systems. Experiments using nude mice receiving implants of pancreatic cancer cells and human squamous carcinoma cells showed decreases in cancer proliferation following laser PDT using hypericin (Chung et al. 2000; Liu et al. 2000; Barnes, Anderson, and Phillipson 2001).

PDT with hypericin promises to treat both nonmelanoma and melanoma skin cancer cells. A pilot study conducted by Kacerovská et al. (2008) found that topical application of H. perforatum extract followed by irradiation with red light induced partial response in patients suffering from actinic keratosis, basal cell carcinoma (BCC), and Bowen's carcinoma in situ. However, all patients complained of burning and pain sensations during irradiation (Kacerovská et al. 2008). When working with cultured melanoma cells, Davids et al. (2008) found that ultraviolet A (UVA)-activated hypericin led to cell death, but only when cells were exposed to a higher dose of 3 μM for 4 hours. Interestingly, hypericin was found to kill melanoma cells via two mechanisms that depended on pigmentation. In pigmented cells, hypericin increases the concentration of reactive oxygen species that cause melanosomes to leak toxic melanin precursors into the cytoplasm, resulting in necrotic death. In contrast, intracellular accumulation of hypericin induces a mitochondrial-associated

caspasedependent apoptotic mode of cell death in nonpigmented melanoma cells (Davids et al. 2008).

Hostanska et al. (2003) showed that hyperforin and hypericin work synergistically to impede the growth of leukemic (K562, U937) cells. Additional studies reveal that use of hypericin alone has only a weak inhibitory effect on cancerous cell growth, whereas methanolic extract of SJW together with hypericin leads to long-lasting inhibition of cell growth, induces apoptosis, and decreases phototoxicity (Roscetti et al. 2004; Schmitt et al. 2006). Although hyperforin and hypericin both show promise as anticancer agents, more research is clearly needed to evaluate their efficacy, mode of action, and adverse interactions.

11.6.4 Antioxidant And Neuroprotective Properties

Recent research shows that extracts of H. perforatum decrease oxidative stress and consequently prevent neurotoxicity, inflammation, and gastrointestinal problems. Flavonoid-rich extracts of H. perforatum (FEHP) are effective against hydrogen peroxide-induced apoptosis in PC12 cells (a cell line derived from the pheochromocytoma of the rat adrenal medulla). Standard extracts of H. perforatum can prevent DNA fragmentation and shrinkage of cells as a result of hydrogen peroxide activity (Lu et al. 2004). Thus, FEHP may effectively treat oxidative stress-related neurodegenerative disorders such as Parkinson's and Alzheimer's diseases (Zou et al. 2010).

Silva et al. (2008) found that the flavonols quercetin and kaempferol provide neuroprotective action by decreasing oxidation of the mitochondrial lipid membrane and maintaining mitochondrial transmembrane electric potential. Conversely, they noted that biapigenin primarily affects mitochondrial bioenergetics and lowers the ability of mitochondria to absorb calcium. Studies performed by Mohanasundari et al. (2006) reported that H. perforatum extract led to the inhibition of MAO-B activity and decreased astrocyte activation in striatal area of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mice. Thus, H. perforatum serves as a neuroprotective agent against MPTP-induced Parkinson's disease in mice (Mohanasundari and Sabesan 2007). Additional studies showed that the combined use of bromocriptine and H. perforatum extract significantly increased dopamine and 3,4-dihydroxyphenylacetic acid, a metabolite of dopamine, in MPTP-induced Parkinson's disease in male Swiss albino mice (Yoshitake et al. 2004; Mohanasundari et al. 2006).

Extracts of SJW protect against cell death caused by amyloid P peptides (Abeta) that form plaques in the brains of those suffering from Alzheimer's disease. Silva et al. (2004) found that ethanolic extracts and those containing flavonol glycosides, flavonol, and biflavone aglycones decreased lipid peroxidation and cell death in rat cultured hippocampal neurons. Flavonoids also enhance survival of microglia (cells that phagocytize foreign bodies in the central nervous system [CNS]) exposed to Abeta (Kraus et al. 2007). Flavonoids decreased formation of amyloid-induced reactive oxygen species in microglia. The flavanols (+)-catechin and (−)-epicatechin from H. perforatum increased cell viability and membrane fluidity of microglia (Kraus et al. 2007). Hyperforin also has been reported to disaggregate amyloid deposits in a dose- and time-dependent manner, thus preventing Abeta-induced neurotoxicity (Dinamarca et al. 2006). Hence, various components found in extracts of H. perforatum may actively combat Alzheimer's disease by mediating Abeta toxicity.

Rats subjected to chronic restraint stress had better recognition memory and working memory, and had significantly enhanced recall of passive avoidance behavior when administered extracts of H. perforatum compared to controls not receiving the extracts (Trofimiuk et al. 2005, 2006; Trofimiuk and Braszko 2008). The herb counteracted the negative effects of stress on cognitive function, and significantly improved hippocampus-dependent spatial working memory (Trofimiuk and Braszko 2008). On the other hand, although H. perforatum has an antiamnestic effect, studies conducted by Khalifa (2005) and Tadros et al. (2009) proved that SJW decreases prepulse inhibition (PPI) of startle response. Prepulse inhibition is important to filtering sensory information, and disruption of PPI is evident in schizophrenia and Huntington's disease (Khalifa 2005). The SJW extract decreased PPI response possibly through enhancing the transmission of monoaminergic (dopaminergic, serotonergic, and noradrenergic) neurotransmitters in the brain stem, thalamus, cortex, and/or hippocampus (Khalifa 2005). Disruption of PPI was found when SJW was administered on both acute (500 mg/kg for 1 day) and chronic (200 mg/kg for 3 days) regimens. Administration of hyperforin similarly elicited disruption of PPI (Tadros et al. 2009). These results suggest that SJW may have limited utility in treatment of cognitive disturbance disorders such as Huntington's and other psychotic diseases.

Sanchez-Reus et al. (2007) found that SJW extracts decreased oxidative stress in the brains of rats treated with the pro-oxidant rotenone. The effects were attributed to liposomal quercetin that significantly preserved the activities of antioxidant enzymes found in the brain tissue. These results led Sanchez-Reus et al. (2007) to conclude that standardized extracts of H. perforatum could be a treatment of choice for depressed elderly patients showing degenerative disorders associated with elevated oxidative stress.

11.6.5 Anti-Inflammatory Activity

H. perforatum shows promise as an anti-inflammatory agent. Rats fed doses of SJW showed decreased levels of blood and bowel enzymes associated with colonic inflammation (Dost et al. 2009), and had lower incidences of gastric ulcers (Cayci and Dayioglu 2009). Sosa et al. (2007) found that lipophilic extracts of H. perforatum had greater anti-inflammatory activity than did ethylacetic or hydroalcoholic extracts. Quercetin and I3,II8-biapigenin, the two major oil extracts of SJW, showed particular anti-inflammatory and gastroprotective activity (Zdunic et al. 2009).

Three mechanisms for the anti-inflammatory response of SJW have been proposed. Tedeschi et al. (2003) found that SJW extracts inhibited the expression of proinflammatory genes like cyclooxygenase-2, interleukin 6, and inducible nitric oxide synthase (iNOS). Detailed experiments on the latter system found that H. perforatum extracts decreased the activity of janus kinase 2, leading to a series of reactions that inhibited the downregulation of signal transducer and transcription (STAT)-1 α DNA binding, further disrupting gene transcription (Tedeschi et al. 2003). Hammer et al. (2007) found that pseudohypericin and hyperforin inhibited production of the inflammatory agent prostaglandin E2 (PGE2). A subsequent ethanol fractionation of H. perforatum extract revealed that four major compounds—chlorogenic acid, amentoflavone, quercetin, and pseudohypericin—acted together to

decrease the inflammation caused by PGE2 (Hammer et al. 2008). This four-component system apparently worked only when pseudohypericin was activated in the presence of light. H. perforatum extract also decreased inflammation in experimental mice given carrageenan-induced pleurisy (Menegazzi et al. 2006). Extracts acted at multiple levels, particularly with the inhibition of nuclear factor κB (NF-κB) and STAT-3 (Menegazzi et al. 2006).

11.6.6 Effects as a Wound-Healing Agent

As noted in Section 11.3, H. perforatum extract has been used over thousands of years as a wound-healing agent. Controlled studies investigating this claim are surprisingly sparse. Ozturk et al. (2007) found that chicken embryonic fibroblasts exposed to SJW extract demonstrated enhanced collagen production, followed by the polygonal shape activation of fibroblast cells that is responsible for wound closure.

11.6.7 Effects on Reducing Opium Dependence

Hydroethanolic crude extract of H. perforatum demonstrated antinociceptive effect against acetic acid-induced abdominal constriction assay in mice, similar to that of opium. This indicates that H. perforatum may act by activating the opioid receptors without causing withdrawal symptoms (Subhan et al. 2007). Feily and Abbasi (2009) reported that H. perforatum decreased the symptoms of opiate withdrawal in adult Wistar rats. The effectiveness of H. perforatum was determined to be equivalent to clonidine, an FDA-approved medication for treating withdrawal symptoms. Thus, H. perforatum may effectively treat opiate withdrawal symptoms in humans (Feily and Abbasi 2009).

11.7 ADVERSE EFFECTS AND INTERACTIONS WITH OTHER DRUGS

As with any pharmacologically active substance, although treatments involving SJW are generally safe, adverse effects can arise either when it is used alone or, especially, in conjunction with other medications.

11.7.1 Adverse Effects

As noted in Section 11.6.1.2, normal dosages of SJW have relatively few side effects. In general, the most common adverse effects are gastrointestinal symptoms, allergic reactions, dizziness, confusion, restlessness, lethargy, and dryness of the mouth (Barnes, Anderson, and Phillipson 2001; Greeson, Sanford, and Monti 2001). These effects are generally mild, moderate, or transient (Ernst et al. 1998). Meta-analyses of clinical trials revealed that reports of adverse effects and drop-out rates were less than 2.5% for patients receiving SJW, far lower than for those receiving conventional antidepressants (Ernst et al. 1998; Schulz 2006). Extracts have also been found to lack genotoxic potential and mutagenic activity, based on in vivo and in vitro studies (Barnes, Anderson, and Phillipson 2001). However, isolated instances of acute toxic neuropathy and induced mania have been reported (Bove 1998; Nierenberg et al. 1999). Hypericin has a unique phototoxic effect that can result in photodermatitis when taken in high doses. The toxic effects are attributed to an acidification of the surrounding environment caused by the transfer of hydrogen between hydroxyl groups on receiving light energy (Fehr, McCloskey, and Petrich 1995; Sureau et al. 1996). Excessive cutaneous phototoxicity was observed with high doses of hypericin (0.5 mg/kg of

body weight) associated with AIDS treatments (Gulick et al. 1999). Normal doses of SJW taken for mild depression do not have any significant associated phototoxic effects (DerMarderosian and Beutler 2002; Jellin et al. 2002).

Recent research using in vitro approaches suggests that use of SJW may have phototoxic effects on the eye. Human lens epithelial cells (He et al. 2004) and human retinal pigment epithelial cells (hRPEs; Wielgus et al. 2007) were both damaged by exposure to a combination of hypericin and light in the visible or UV ranges. Schey et al. (2000) found that hypercin and light combined to cause damage to lens α-crystallin proteins. However, no adverse effects of SJW to vision have been reported in a clinical setting. Nonetheless, individuals taking SJW should take normal precautions to protect their eyes against excessive exposure to sunlight.

11.7.2 Drug Interactions: Overview

Although adverse drug reactions are relatively rare for individuals taking SJW as a stand-alone supplement, the daily dose becomes an issue of concern when the user is also taking other medications that potentially interact with the constituents of SJW. Preparations made from the species have been reported to interact with a diverse selection of drugs that are explored in excellent reviews (Barnes, Anderson, and Phillipson 2001; Greeson, Sanford, and Monti 2001; Izzo 2004; Mannel 2004; Di et al. 2008; Zhou and Lai 2008). The herb in some cases has been shown to increase the effectiveness of other compounds when taken together. This increase may be helpful to the individual or may increase the compound's effects to toxic levels. Conversely, the herb may decrease or even cancel the effects of other drug constituents (Parker et al. 2001). Mechanisms responsible for the interactions have been clarified over the past 15 years. As has been widely reported (e.g., Izzo 2004; Di et al. 2008; Zhou and Lai 2008), SJW extract induces P-glycoprotein (P-gp) along with a series of drug-metabolizing enzymes, the cytochrome P450s (CYPs), including CYP2C9 and CYP3A4.

11.7.2.1 P-glycoprotein

P-glycoprotein is an adenosine triphosphate (ATP)-binding cassette (ABC) transporter belonging to the multidrug resistance/transporter associated with antigen processing (MDR/TAP) subfamily (Higgins 1992; Garrigues, Escargueil, and Orlowski 2002). It is distributed and expressed in the intestinal epithelium, hepatocytes, renal proximal tubular cells, and capillary endothelial cells. As a member of the MDR/TAP subfamily, it is involved in multidrug resistance and transports various molecules across extra- and intracellular membranes (Dean, Hamon, and Chimini 2002). In humans, P-gp is encoded by the MDR1 (ABCB1) gene (Ueda et al. 1987; Zhou 2008). The encoded protein is an ATP-dependent drug efflux pump for xenobiotic constituents with broad substrate specificity.

Extracts of SJW have been widely observed to induce P-gp expression. These studies have been conducted in vitro, in rats and mice, and clinically (Durr et al. 2000; Hennessy et al. 2002; Dresser et al. 2003). Expression has been observed in P-gp from various organs and tissues including intestinal cells (Durr et al. 2000), peripheral blood lymphocytes (Hennessy et al. 2002), and intestinal carcinoma cells (Perloff et al. 2001). Hypericin was the main constituent responsible for the stimulation of P-gp activity (Mannel 2004). Conversely, Tian

et al. (2005) found that hyperforin increased the expression of P-gp in LS 180 intestinal carcinoma cells, whereas hypericin had no effect. Removal of SJW resulted in a restoration of normal P-gp level within 48 hours (Tian et al. 2005).

11.7.2.2 Cytochrome P450

The CYP comprises a large and diverse superfamily of hemoprotein enzymes common to nearly all taxa. They metabolize multiple exogenous and endogenous substrates and catalyze a diverse array of reactions, especially in the liver, where they metabolize drugs and toxic compounds (von Moltke et al. 1995; Zhou 2008). A wide variety of CYP isotypes occur within individual organisms and across taxa. The nomenclature involves use of a three-character code following the CYP prefix. The first character is a number that refers to the family, the following capital letter indicates the subfamily, and the second number refers to the specific gene (Nelson et al. 1993). Thus, the common CYP3A4 belongs to family 3, subfamily A, gene 4.

The SJW extract has been widely found to induce a variety of CYP isotypes. Increases in the activity of CYP3A, and especially CYP3A4, are particularly well documented (reviewed by Madabushi et al. 2006; Whitten et al. 2006; Zhou and Lai 2008). Gurley et al. (2002) found increases in CYP3A4 to be especially noticeable in females. Specific cell types in which induction has been noticed include intestinal and hepatic cells from mice, rats, and humans (Durr et al. 2000; Moore et al. 2000; Bray et al. 2002b; Cantoni et al. 2003; Komoroski et al. 2004). The SJW extracts were also shown to induce other CYP isotypes including CYP1A2 (Nebel et al. 1999), CYP2C9 (Obach 2000; Komoroski et al. 2004), CYP2C19 (Wang et al. 2004), CYP2D6 (Obach 2000), and CYP2E1 (Bray 2002b; Gurley et al. 2002). Wenk, Todesco, and Kráhenbühl (2004) found that extracts successfully induced CYP1A2 in females, but not in males. Conversely, extracts failed to induce or inhibited expression of other isotypes of CYP, including CYP1A or CYP2D6 (Bray et al. 2002b; Komoroski et al. 2004; Wenk, Todesco, and Kráhenbühl 2004). Interestingly, Obach (2000) found that SJW inhibited CYP3A4, but only in an in vitro system. When working with isolated hepatocytes, Komoroski et al. (2004) found that acute administration of hyperforin at 5 and 10 μM inhibited CYP3A4 activity.

Of the various SJW constituents, hyperforin appeared to be the most effective in activating CYP isotypes (Komoroski et al. 2004; Pal and Mitra 2006; Whitten et al. 2006). Pal and Mitra (2006) also found that the flavonoids kaempferol and quercetin showed enhanced expression of CYP3A4 messenger ribonucleic acid (mRNA) in Caco-2 cells. In contrast, hypericin had no effect on any of the CYP isotypes tested (Komoroski et al. 2004). The ability of hyperforin to induce CYP3A4 and other isotypes depends on the duration and dosage of exposure. Bray (2002a, b) observed no induction of hepatic CYP2E1 and CYP3A in mice after 4 days of treatment, whereas 3 weeks of dosing led to increased expression of both genes. In humans, the effect of CYP3A induction is strongly influenced by SJW dose (Mueller et al. 2006). Likewise, Mueller et al. (2009) found that administration of an SJW product with a low hyperforin content led to clinically irrelevant levels of induction of CYP3A. In their review, Whitten et al. (2006) recommend more studies should be conducted to determine whether decreased CYP3A induction occurs after giving low-dose hyperforin extracts.

A mechanism by which extracts of SJW, particularly hyperforin, induce some cytochromes has been proposed (Figure 11.3). The pathway starts with the human pregnane X receptor (PXR), which is a member of the orphan nuclear receptor family (Moore et al. 2000; Mannel 2004), and is encoded by the NR1I2 gene (Zhou and Lai 2008). The PXR functions as a transcriptional regulator for several genes, including those that code for the CYP enzymes and various drug transporters such as P-gp, which is involved in the detoxification and transport of multiple xenobiotics (Wang et al. 2004; Zhou and Lai 2008). Intracellular hyperforin binds with PXR to produce a functional complex that binds to the pregnane response element (PRE) of CYP3A4, CYP2B6, and MDR1 genes. The PXR/PRE complex then activates and initiates the targeted genes, producing active CYP3A4, CYP2B6, and P-gp (Zhou and Lai 2008). Because of this process, SJW has significant interaction with any drug metabolized by CYP3A4 and CYP2B6 or transported by P-gp.

FIGURE 11.3. Diagram of the pathway of gene induction by the St.

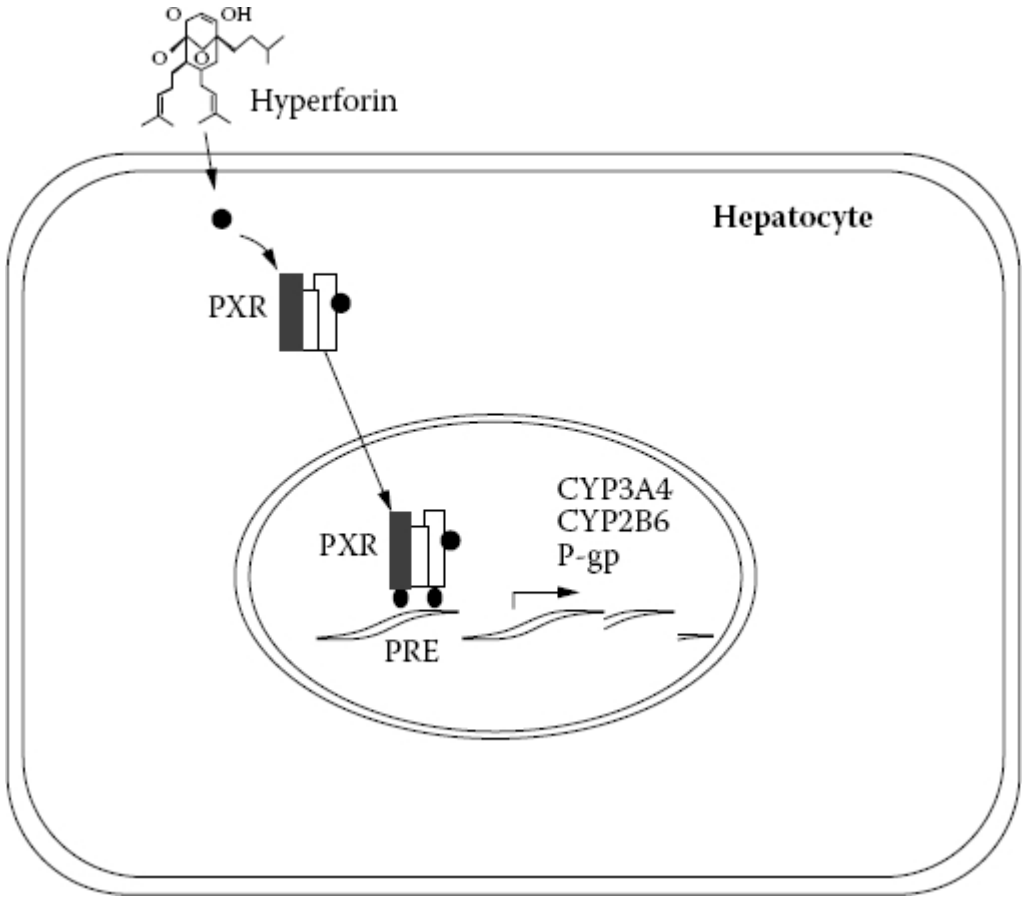


Diagram of the pathway of gene induction by the St. John's wort constituent, hyperforin, in a hepatocyte. Hyperforin enters the cell and binds to the human pregnane X receptor (PXR) in the cytoplasm. The complex enters the nucleus, binding with the pregnane (more...)

11.7.2.3 Specific Drug Interactions

In this section, specific drugs reported to interact with SJW are reviewed briefly. Readers seeking additional details should consult the excellent reviews available, including, but not limited to, those by Henderson et al. (2002), Izzo (2004), Di et al. (2008), and Zhou and Lai (2008).

Fexofenadine is a nonsedating antihistamine used for treating allergic rhinitis and urticaria (Markham and Wagstaff 1998). Clinical studies have found that the effects of SJW on fexofenadine vary depending on dose and duration. A single treatment caused a 45% increase in the maximum plasma concentration, presumably by inhibiting P-gp (Wang et al. 2002). Conversely, a 12-day treatment caused a 35% decrease in Cmax (maximum plasma concentration; Wang et al. 2002) and a 60% increase in oral clearance of fexofenadine (Dresser et al. 2003), suggesting P-gp induction.

Digoxin and other members of the digitalis family of cardioactive drugs from the Digitalis (foxglove) plant also show side effects when used in conjunction with SJW. Whereas a single dose of SJW had no measureable impact on digoxin pharmokinetics, a 10-day treatment of SJW extract showed decreased Cmax and AUC (area under the plasma concentration-time curve) of digoxin compared to placebo (Johne et al. 1999). However, Mueller et al. (2004) and Arold et al. (2005) found that patients who were administered low-hyperforin preparations of SJW had little in the way of decrease in digoxin AUC. Thus, the pharmacokinetic effect is apparently due to the induction of intestinal P-gp caused by multiple doses of SJW high in hyperforin.

The anticancer drug imatinib mesylate (Gleevec) is a strong inhibitor of specific tyrosine kinases that promote tumor cell proliferation (Collins and Workman 2006). Imatinib is transported by P-gp and metabolized by CYP3A4 and CYP3A5 (Peng, Lloyd, and Schran 2005). Two studies have shown SJW interacts with imatinib. Frye et al. (2004) found that 2 weeks of SJW treatment on 10 healthy subjects decreased the AUC by 32%. When working with 12 healthy subjects receiving SJW extracts, Smith et al. (2004), likewise, found increased clearance and reduced AUC and Cmax for imatinib.

SJW has been shown to affect the pharmacokinetics of the drug amitriptyline, a tertiary amine tricyclic antidepressant metabolized in the liver by CYP3A4, CYP2C19, and CYP2D6 (Venkatakrishnan, von Moltke, and Greenblatt 1999). A clinical study of 12 patients taking both SJW and amitriptyline exhibited a decrease in AUC as well as decreases in plasma concentrations (Johne et al. 2002).

Ivabradine is a selective sinus node channel inhibitor that decreases cardiac pacemaker activity, allowing for slower heart contractions and more time for blood flow. Intestinal and hepatic CYP3A4 metabolizes ivabradine (Zhou and Lai 2008). In 12 volunteers given SJW for 14 days, the AUC of ivabradine was lowered by 61.7%, while the maximum plasma concentration was lowered by 52.9% (Portoles et al. 2006).

Cyclosporin and tacrolimus are immunosuppressants commonly used to prevent the body from rejecting transplanted organs (Akhlaghi and Trull 2002; Zhou and Lai 2008). Cyclosporin and tacrolimus are metabolized by CYP3A4 and P-gp (Hebert 1997; Lown et al. 1997; Niwa et al. 2007; Zhou 2008). Concerns over the ability of SJW to interfere with cyclosporin first

surfaced with clinical reports of patients receiving transplants (Barone et al. 2000; Mai et al. 2000; Ruschitzka et al. 2000; Ernst 2002). In those cases, patients demonstrated improved immunosuppression once SJW therapy was stopped. Larger studies involving 30 (Breidenbach et al. 2000) and 11 (Bauer et al. 2003) recently transplanted patients found that plasma levels of cyclosporin dropped when receiving SJW treatment, and that cyclosporin levels rose sharply when SJW was stopped. Mai et al. (2003) found that SJW extracts containing high levels of hyperforin induced lower plasma Cmax and AUC than extracts having low hyperforin content. Other studies indicate that patients on other immunosuppressants, such as tacrolimus, experience similar effects (Mai et al. 2003).

Antihypertensive agents have also been shown to interact with SJW. The calcium channel blocker, verapamil, is first-pass metabolized by CYP3A4 (Tannergren et al. 2004). Eight males administered SJW for 14 days showed a 78-80% decrease in AUC and a 76-78% decrease in the Cmax of verapamil, compared to the control (Tannergren et al. 2004). Clinical studies on nifedipine (Wang et al. 2007) and talinolol (Schwarz et al. 2007) revealed similar decreases in their AUC and Cmax values, although the latter may be attributed more to P-gp than CYP3A4 induction.

SJW has been shown to interact with benzodiazepine sedatives, including quazepam, alprazolam, and midazolam (Zhou and Lai 2008). All are metabolized by CYP3A4, although other CYPs play a role (Gorski et al. 1994; von Moltke et al. 1996; Miura and Ohkubo 2004). Studies conclude that interactions with SJW from a 14-day treatment decrease the AUC and Cmax values for the drugs as well as reduce oral clearance and bioavailability (Kawaguchi et al. 2004). The proposed mechanism for the decreased pharmacokinetics is CYP3A4 induction, although SJW did not reduce the sedative effect of quazepam.

The use of SJW may decrease concentrations and nullify the effect of steroid contraceptives that are substrates for—and inducers of—CYP3A4 (Thummel and Wilkinson 1998). Moreover, the major component of oral contraceptives, ethinylestradiol, is metabolized by CYP3A4 (Guengerich 1988). An analysis conducted by Hall et al. (2003) found that SJW administered concomitantly with a combination oral contraceptive pill containing ethinylestradiol and norethindrone to 12 healthy premenopausal women caused an increase in the oral clearance of norethindrone and a significant reduction in the half-life of ethinylestradiol, consistent with increased CYP3A activity. However, they found that SJW did not affect the serum concentrations of follicle-stimulating hormones, luteinizing hormones, and progesterone. The authors noted a higher incidence of breakthrough bleeding during the SJW administration phase, a problem also observed by others (Ernst 1999; Yue, Bergquist, and Gerden 2000; Schwarz, Buschel, and Kirch 2003). Breakthrough bleeding often leads to the discontinuation of oral contraceptive use, occasionally resulting in unintended pregnancy (Rosenberg and Waugh 1998). Once SJW was discontinued, menstrual cycles returned to normal; however, alternate forms of birth control are suggested if the use of SJW is continued (Schwarz, Buschel, and Kirch 2003).

SJW can decrease the serum levels of two main classes of anti-HIV compounds: (1) protease inhibitors and (2) nonnucleoside reverse transcriptase inhibitors (NNRTIs), when taken concomitantly. In both cases, the effect is largely due to induction of CYP3A4 (Zhou 2008). An

analysis of eight healthy subjects found a 57% decrease in the plasma concentration of the protease inhibitor indinavir (Piscitelli et al. 2000). A follow-up study by Ho et al. (2009) found that SJW extract administered to rats stimulated the ability of hepatic and intestinal CYP3A to lower indinavir plasma levels. Decreases in NNRTIs, particularly nevirapine and lamivudine, were also found when coadministered with SJW. In contrast, a study by L'Homme et al. (2006) found that SJW did not lower the concentration of nevirapine when administered to a small group of healthy women.

Warfarin and related compounds are widely used anticoagulants synthesized from coumarin, a benzopyrone found naturally in several plants (Runciman et al. 2002; Yarnell and Abascal 2009). Warfarin is a vitamin K inhibitor, and is used to treat clotting disorders like thrombosis and embolism, as well as myocardial infarction, atrial fibrillation, and stroke (Bovill, Fung, and Cushman 2004). Claims of interactions between SJW and coumarin-derived anticoagulants were first made in cases observed in Sweden (Ernst et al. 1998 Yue, Bergquist, and Gerden 2000). Subsequent controlled studies found that healthy males given SJW had higher clearances of anticoagulant than the control group (Jiang et al. 2004; Jiang, Blair, and McLachlan 2006). Since at least one enantiomer of warfarin is metabolized by CYP2C9, Zhou and Lai (2008) suggest the induction of that enzyme by either hyperforin or hypericin in SJW contributes to the clearance of warfarin.

The antifungal agent, voriconazole, is metabolized mainly by CYP2C19, and also by CYP3A4 and CYP2C9 (Hyland, Jones, and Smith 2003). In a study of 16 men, concomitant SJW treatment for 15 days was found to decrease the AUC of voriconazole by 59%, as well as increasing its oral clearance (Rengelshausen et al. 2005).

SSRIs are commonly used compounds to treat depression, anxiety, and personality disorders, and are primarily metabolized by CYP2D6 (Zhou and Lai 2008). The use of SJW with antidepressants containing paroxetine, sertraline, venlafaxine, nefazodone, clomipramine, and others can create serotonin syndrome, which is characterized by shivering, tachycardia, hypertension, hyperactive bowel sounds, diaphoresis, and hyperthermia (Gordon 1998; Lantz, Buchalter, and Giambanco 1999; Beckman, Sommi, and Switzer 2000; Parker et al. 2001; Boyer and Shannon 2005). Research suggests that CYP and P-gp induction is not the underlying mechanism behind the interaction. The SSRIs are mainly metabolized by CYP2D6, but the cause of the additive effect is uncertain (Zhou and Lai 2008). However, the combination of SSRIs and SJW should be avoided until the safety profile can be fully defined.

The use of SJW concomitantly with other herbs taken as dietary supplements may lead to other interactions. The documented cases of concomitant use of SJW with herbs that have sedative properties where the combination may have enhanced both the therapeutic as well as the adverse effects include interactions with calamus, canendula, California poppy, catnip, capsicum, celery, couch grass, elecampane, Siberian ginseng, German chamomile, goldenseal, gotu kola, hops, Jamaican dogwood, kava, lemon balm, sage, sassafras, scullcap, shepherd's purse, stinging nettle, valerian, wild carrot, wild lettuce, ashwaganda root, and yerba mensa (Jellin et al. 2002).

11.8 FUTURE RESEARCH NEEDS

Despite the many dozens of clinical, in vivo, and in vitro studies conducted on the medicinal attributes of SJW, unanswered questions remain regarding its therapeutic value, mechanisms of action, and adverse interactions. A particularly perplexing question relates to its therapeutic value in treating depression. The literature over the past 15 years contains conflicting evidence regarding the usefulness of the species in treating major depression. What is more, the persistent difference in demonstrated efficacy between studies conducted in German-speaking and non-German-speaking countries remains an issue. We agree with Linde, Berner, and Kriston (2009) that future work must focus on resolving this apparent contradiction. Additional research is needed regarding the therapeutic value of SJW in treating other diseases like cancers, skin wounds, and opium dependence. Moreover, the potential of specific constituents like hypericin, hyperforin, and flavonoids deserve further elucidation.

Regarding adverse impacts, we note that reports of interactions with some drugs (e.g., warfarin) are based on repeated independent studies involving clinical observations, controlled assessments of dozens of individuals, and in vivo tests. Conversely, the evidence for interactions with a few other drugs (e.g., ivabradine, protease inhibitors, vorconizole) appears to be based on a single study of perhaps a dozen individuals. Further work to at least determine replicability seems in order. We also agree with Zhou and Lai (2008) that additional research is needed to investigate whether different formulations of SJW (e.g., low vs. high hyperforin content) result in different adverse interactions.

11.9 CONCLUSIONS

SJW has a long history of use as an herbal treatment for a variety of ailments. Over the past 20 years, it has become a mainstream alternative treatment for depression, as well as holding promise as a therapy for cancer, inflammation, bacterial and viral infections, and other disorders. Thanks to its popularity, the effectiveness of SJW has been intensively studied since the mid-1980s. These studies have focused on the pharmacology of its constituents and on clinical trials. Pharmacological investigations show that extracts of SJW do have neuroactive properties. Interestingly, such properties appear to derive primarily from the constituent hyperforin, rather than from hypericin, which has been investigated for a longer period of time.

Numerous studies conducted in Germany in the 1990s indicate that individuals showing mild to moderate depression who take SJW show improvement in mood at rates higher than those taking a placebo. Moreover, the rates of improvement were seen as being similar to those experienced by individuals taking synthetic antidepressants. However, the clinical

studies comparing the effects of SJW against synthetics were criticized on the basis of their short durations of study and a claim that the dosage of the synthetics was below the typical dosage. Studies conducted in the United States in 2001 and 2002 failed to show a clear benefit of SJW over a synthetic antidepressant and a placebo. However, studies and meta-analyses conducted since then point to the efficacy of SJW in treating all forms of depression. It is interesting to note that the greatest clinical success for the herbal remedy was achieved in Europe, where the use of herbal therapies is standard, compared to the findings for the remedy in the United States, where reliance on synthetic medicines is highest.

SJW does appear to be an effective treatment for other disorders, particularly some skin ailments, inflammation, and certain forms of cancer. It has demonstrated antibacterial and antiviral activity, although its promise as an anti-HIV therapy is questionable. Recently, its antioxidant and neuroprotective properties have become recognized. Most clinical studies show SJW to be relatively safe, especially at typical dosages. However, high dosages might lead to phototoxicity in susceptible individuals. Extracts of SJW do appear to interact with other medications, especially drugs that impact liver and intestinal enzyme function. Therefore, individuals taking SJW along with other medications should be aware of such potential drug interactions, and should report their use to their health-care providers.

As with any herbal remedy, any individual taking SJW is advised to consult his or her physician to ascertain that the herb is the best course of action when seeking the most efficacious remedy for any condition.

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