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REVIEW

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St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological, and clinical literature

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Abstract *Rationale:* St. John's wort (*Hypericum perforatum*) has recently gained popularity as an alternative treatment for mild to moderate depression. Given the current widespread use of this herbal remedy, it is important for medical professionals to understand the potential pharmacological pathways through which *Hypericum* may exert an antidepressant effect. *Objectives:* (1) To review the current pharmacological, toxicological, and clinical literature available on *Hypericum*, and (2) to provide a synthesis of this information into a form that may be easily used by health care providers. *Method:* A comprehensive review of the recent scientific literature (January 1990–March 2000) was performed using the following electronic databases and reference publications: MEDLINE, The Cochrane Library, HealthSTAR, Current Contents (all editions), European Scientific Cooperative on Phytotherapy monographs, German Commission E monographs, and the Physicians' Desk Reference for Herbal Medicines, 1st edition. *Results:* One hundred and seven (107) publications in the English language and three publications in German were included in the review. Collectively, the data suggest that therapeutic preparations of *Hypericum* extract appear to exert potentially significant pharmacological activity within several neurochemical systems believed to be implicated in the pathophysiology of depression. However, little information exists regarding the safety of *Hypericum*, including potential herb–drug interactions. *Conclusions:* Additional research on the pharmacological and biochemical activity of *Hypericum* and its several bioactive constituents is necessary to further elucidate the mode(s) of antidepressant action. Given what is currently known and unknown about the biological properties of *Hypericum*, those who choose to use this herb should be closely monitored by a physician.

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Abbreviations *DSM* Diagnostic and Statistical Manual of Mental Disorders · *ESCOP* European Scientific Cooperative on Phytotherapy · *ICD* International Classification of Diseases · *NCCAM* National Center for Complementary and Alternative Medicine · *PDR* Physicians' Desk Reference

Introduction

Hypericum perforatum is a perennial herb indigenous to Europe, western Asia, and northern Africa (PDR for Herbal Medicines 1998). The plant can now be found throughout the United States, and is distinguished by its golden yellow flowers. The flowers contain a red liquid comprised of complex, biologically active compounds. St. John's wort, which consists of the dried, aboveground portions of *Hypericum*, is sold as a nutritional supplement (NCCAM 1999). The botanical is commercially available in tablet, capsule, tea, and tincture forms.

Hypericum has been used as a medicinal plant for centuries. Oily *Hypericum* preparations may be applied externally to treat minor burns, wounds, inflammation of the skin, and nerve pain (Blumenthal et al. 1998). Internally, the herbal preparation is indicated for the treatment of anxiety and depressive episodes (PDR for Herbal Medicines 1998). Today, *Hypericum* is used widely in Germany for the treatment of depression where it is prescribed approximately 20 times more often than fluoxetine, one of the most highly prescribed antidepressants in the United States (NCCAM 1999). In the U.S., *Hypericum* is increasingly used as an over-the-counter remedy by a significant portion of the lay population for the treatment of depression. In 1998, *Hypericum* was expected to garner $400 million in sales in the U.S. (NCCAM 1999) and an estimated $6 billion in Europe (Ernst 1999), despite a lack of consensus regarding its efficacy among the medical community and the absence

of standardization guidelines in the U.S. Furthermore, the specific mode(s) of purported antidepressant activity are not well defined. There is some evidence that *Hypericum* may exert a significant influence on catecholamine neurotransmission via known pathways, including: (a) inhibition of neurotransmitter metabolism, (b) modulation of neurotransmitter receptor density and sensitivity, and (c) synaptic reuptake inhibition. Similar to conventional antidepressant pharmacology, these mechanisms may ultimately lead to increased synaptic availability of the neurotransmitters believed to be implicated in clinical depression, namely serotonin (5-HT), norepinephrine (NE), and dopamine (DA).

Method

A comprehensive review of the recent scientific literature (January 1990–March 2000) was performed using the following electronic databases and reference publications: MEDLINE (National Library of Medicine, Bethesda), The Cochrane Library (Update Software, San Diego), HealthSTAR (National Library of Medicine, Bethesda), Current Contents (Institute for Scientific Information, Philadelphia), ESCOP Monographs on the Medicinal Uses of Plant Drugs, The Complete German Commission E Monographs, and the PDR for Herbal Medicines, 1st edition. Search terms used were: *Hypericum*, St. John's wort, adverse effects, drug interactions, pharmacology, and toxicology. Additional papers were obtained by hand-searching bibliographic references. Studies were reviewed if they pertained to the biochemistry, pharmacology, and/or toxicology of *Hypericum perforatum*. Selections were limited to the English language.

Overview of the clinical literature

In 1995, a systematic, criteria-based review of 12 randomized controlled trials (RCTs) of *Hypericum* suggested that the herb was superior to placebo and equally effective as standard medication in alleviating symptoms of depression (Ernst 1995). However, all studies reviewed were performed in Germany where individualized, subjective factors are commonly used to assess psychiatric outcomes as opposed to standardized, objective measures (Kunze and Priebe 1998). It was concluded that additional studies with rigorous methodology were necessary in order to elucidate the safety and efficacy of the extract. In 1996, a meta-analytic review of 23 RCTs involving 1757 outpatients with mild to moderate depression concluded that *Hypericum* was: (a) nearly 3 times more efficacious than placebo, (b) as effective as some tricyclic antidepressants (TCAs), and (c) safer with respect to incidence and severity of side effects commonly associated with TCA drug treatment (Linde et al. 1996). However, Deltito and Beyer (1998) suggest that these conclusions may be invalid because many of the studies reviewed utilized broad subject inclusion criteria and were often characterized by one or more major methodological flaws. These authors critiqued the recent literature on the use of *Hypericum* in the treatment of depression and highlighted numerous concerns regarding past clinical research studies, including: (1) lack of diagnostic rigor resulting in heterogeneous depressed patient populations, (2) the use of subtherapeutic dosages of TCAs in drug-comparison studies, (3) high placebo responder rates, often indicative of mild, transient depressive episodes, and (4) improper analyses of side effects, or adverse drug reactions (Deltito and Beyer 1998).

A recent meta-analysis of six well-designed clinical trials involving 651 outpatients with mild to moderate depressive disorders revealed *Hypericum* to be only 1.5 times more effective than placebo, yet equally efficacious as compared to low doses of TCAs (for example, amitriptyline, imipramine, maprotiline; Kim et al. 1999). This review also demonstrated that the incidence of side effects associated with *Hypericum* was half the number associated with TCAs. The authors attempted to control for previous flaws in research design by selecting only those studies that compared *Hypericum* to placebo or standard antidepressant treatment in patients classified according to ICD-10, DSM-III-R, or DSM-IV criteria. In addition, all studies reviewed defined treatment effects using the Hamilton Depression Scale. However, despite these safeguards, the authors acknowledged several methodological concerns across these studies, such as psychiatric evaluations conducted by primary care physicians, lack of objective standardized outcome measures, inadequate study duration, and lack of extended follow-up.

Another recent systematic review of eight randomized, double-blind studies of *Hypericum* vs placebo or TCA medication generally supports the results of previous reviews, however this study found that the overall response rate for patients treated with *Hypericum* was 6–18% lower than the response rate for patients treated with a TCA (Gaster and Holroyd 2000). A multicenter RCT sponsored by the National Institutes of Health is currently underway (NCCAM 1997). This trial, the first in the U.S. to investigate the efficacy of *Hypericum* in relation to a selective serotonin reuptake inhibitor (SSRI), will compare *Hypericum* to placebo and sertraline in 336 patients with major depression. The only published study to compare *Hypericum* against an SSRI (fluoxetine, 20 mg/day) found that the herb was equally efficacious in treating elderly patients with mild to moderate depressive episodes (Harrer et al. 1999).

Bioactive constituents

Hypericum contains at least ten classes of biologically active detectable compounds (see Table 1). These constituents often vary in concentration among individual plants. There are several reasons for this including genetic variation within the species and/or adulteration, eco-

Table 1 Biologically active detectable compounds found in St. John's wort (*Hypericum perforatum*). Data extracted from ESCOP monographs (1997), PDR for Herbal Medicines (1998), Cracchiolo (1998), and Nahrstedt and Butterweck (1997). *N/A* Not available, *GABA* gamma-aminobutyric acid

Biochemical class	% Fresh plant[a]	Active constituent	% Fresh plant[a]
Naphthodianthrones	0.03–3.0 (Flowers/buds)	Hypericin	0.09
		Pseudohypericin	0.23
Phloroglucinols	2–5 (Flowers/buds)	Hyperforin	2.0–4.5
		Adhyperforin	0.2–1.8
Flavonoids	12 (Leaves)	Quercetin	2.0
	7 (Stalk)	Hyperoside	0.7
	2–4 (Buds)	Quercitrin	0.5
		Isoquercitrin	0.3
		Rutin	0.3
		Campferol	N/A
		Myricetin	N/A
		Amentoflavone	0.01–0.05
		I3,II8-Biapigenin	0.10–0.50
Procyanidins	12 (Aerial parts)	Procyanidin	N/A
	8 (Flowers/buds)	Catechin	N/A
		Epicatechin polymers	N/A
Tannins	6–15	Tannic acid	N/A
Essential oil	0.06–1.0 (Flowers/leaves)	Terpenes, alcohols	N/A
Amino acids	0.01	GABA	0.0007
		Cysteine	N/A
		Glutamine	N/A
		Leucine	N/A
		Lysine	N/A
		Ornithine	N/A
		Proline	N/A
		Threonine	N/A
Phenylpropanes	0.1	Caffeic acid	0.1
		Chlorogenic acid	<0.1
Xanthones	0.01 (Roots)	Kielcorin, norathyriol	N/A
	0.0004 (Leaves/stem)		
Other water-soluble components	0.5	Organic acids, peptides, polysaccharides	N/A

[a] Relative content is variable and dependent upon genetic variation within the species and/or adulteration, ecological growing conditions, time of harvesting, preparation and processing of sample material, and exposure to light

logical growing conditions, time of harvesting, preparation and processing of sample material, and exposure to light (Nahrstedt and Butterweck 1997; Wagner and Bladt 1994). Despite such variation, approximately 20% of a given plant extract is comprised of bioactive compounds, as verified by standard bioanalytical techniques (Erdelmeier 1998; Nahrstedt and Butterweck 1997; Staffeldt et al. 1994).

Naphthodianthrones, namely hypericin and pseudohypericin, are found in the flowering portions of the plant. Until recently, these two compounds were considered responsible for the purported antidepressant effect of *Hypericum*. Total hypericin content (0.3 mg) has been used for standardization purposes within the botanical industry, however, the proportion of hypericin found in a given commercial extract may range widely, from 0.05–0.30% (Nahrstedt and Butterweck 1997).

Numerous flavonoid compounds, including hyperoside, quercitrin, isoquercitrin, rutin, quercetin, campferol, luteolin, and myricetin, are found in the aboveground portions of the plant, including the leaves, stalk, flowers, and buds. So too are the biflavonoids I3,II8-biapigenin and I3′,II8-biapigenin (amentoflavone). Phloroglucinol compounds, including hyperforin and adhyperforin, are present in the flowers and buds. Procyanidins, tannins, coumarins, amino acids, phenylpropanes, and other constituents exist in the plant as well, although none of these compounds are believed to exert antidepressant bioactivity.

Pharmacological activity and potential mechanisms of antidepressant action

Hypericum (whole plant) extract

In vitro experimentation with *Hypericum* extract has revealed several ways in which this herbal preparation may

Table 2 Central pharmacological activity associated with *H. perforatum* and conventional antidepressant pharmaceuticals. *ACh* Acetylcholine, *BDZ* benzodiazepine, *COMT* catechol-*O*-methyltransferase, *DA* dopamine, *GABA* gamma-aminobutyric acid, *inh.* inhibition, *IP3* inositol triphosphate, *mACh* muscarinic acetylcholine, *MAO* monoamine oxidase, *MAOI* monoamine oxidase inhibitor, *NE* norepinephrine, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *5-HT* 5-hydroxytryptamine (serotonin), ↑ increase, ↓ decrease

Biochemical class (Example)	Monoamine metabolism (µmol/l range)	Receptor affinity (µmol/l range)	Receptor density and sensitivity (D, S)	Synaptic uptake inhibition (µmol/l to nmol/l range)	EEG (λ)
Hypericum extract (LI 160)	MAO inh.[f, g]	5-HT1A[g, h]	↓ β-adrenoceptor[b, j](D)	5-HT[j–n, v]	↑ Delta (ACh)[x, z, cc, dd]
	COMT inh.[f]	GABA-A,B[g] BDZ[g]	↑ 5-HT1A[a, i] (D) ↑ 5-HT2[a, b, i, j] (D)	NE[k, l, n] DA[l, n]	↑ Theta (NE)[x, y] ↑ Alpha-1 (5-HT)[x, bb, cc]
		Adenosine[g] IP3[g] mACh[h] MAO-A,B[g]	↓ NE[k] (S) ↑ Beta-1[x, bb] ↑ Beta-2[y, bb]	↑ Alpha-2 (DA)[bb, dd]	
Napthodianthrones (Hypericin)	MAO inh.[e, o]	σ-opioid[p]	None known	5-HT[c, h] NE[c, h]	None known
Phloroglucinols (Hyperforin)	None known	5-HT3[d, v]	None known	5-HT[l, u, v] NE[l, u] DA[l, u] GABA[u] L-Glutamate[u]	None known
Flavonoids (Quercetin)	MAO inh.[f, q] COMT inh.[f, q]	BDZ (agonist)[r]	None known	None known	None known
Biflavonoids (Amentoflavone)	None known	BDZ (agonist)[s, t]	None known	None known	None known
Xanthones (Kielcorin)	MAO inh.[w] COMT inh.[w]	None known	None known	None known	None known
SSRI[aa] (Fluoxetine)	None known	5-HT1A 5-HT2 α_1-adrenergic Histaminergic mACh	↓ β- adrenoceptor (D) ↓ 5-HT2 (D) ↑ 5-HT1A (S)	5-HT NE DA	↑ Alpha (5-HT)
TCA[bb] (Imipramine)	None known	α_1-adrenergic Histaminergic mACh	↓ β- adrenoceptor (D) ↓ 5-HT2 (D) ↑ 5-HT1A (S)	5-HT NE	↑ Alpha (5-HT)
MAOI[cc] (Phenelzine)	MAO inh.	MAO-A, MAO-B	↓ β- adrenoceptor (D) ↓ α_1-adrenergic (D) ↓ α_2-adrenergic (D) ↓ 5-HT1 (D) ↓ 5-HT2 (D)	None known	↑ Alpha (5-HT)

[a] Chronic daily oral administration
[b] Subchronic daily oral administration
[c] mmol/l range
[d] Unproven; hyperforin antagonizes serotonin-induced (5-HT3 receptor-mediated) increase in heart rate in rats
[e] Impure study sample
[f] Data extracted from Thiede and Walper (1994)
[g] Data extracted from Cott (1997)
[h] Data extracted from Müller and Schäfer (1996)
[i] Data extracted from Teufel-Mayer and Gleitz (1997)
[j] Data extracted from Müller et al. (1997)
[k] Data extracted from Neary and Bu (1999)
[l] Data extracted from Müller et al. (1998)
[m] Data extracted from Perovic and Müller (1995)
[n] Data extracted from Rolli et al. (1995)
[o] Data extracted from Suzuki et al. (1984)
[p] Data extracted from Raffa (1998)
[q] Data extracted from Bladt and Wagner (1994)
[r] Data extracted from Nahrstedt and Butterweck (1997)
[s] Data extracted from Baureithel et al. (1997)
[t] Data extracted from Nielson et al. (1988)
[u] Data extracted from Chatterjee et al. (1998a)
[v] Data extracted from Chatterjee et al. (1998b)
[w] Data extracted from Suzuki et al. (1981)
[x] Data extracted from Schellenberg et al. (1998)
[y] Data extracted from Johnson et al. (1994)
[z] Data extracted from Schulz and Jobert (1994)
[aa] Data extracted from Tollefson and Rosenbaum (1998)
[bb] Data extracted from Dimpfel et al. (1999); Potter et al. (1998)
[cc] Data extracted from Dimpfel et al. (1998); Krishnan (1998)
[dd] Data extracted from Dimpfel and Schombert (1997)

alter monoamine neurotransmission in the central nervous system (Table 2). For example, Thiede and Walper (1994) initially reported 27% inhibition of monoamine oxidase (MAO) activity, and 35% inhibition of catechol-*O*-methyltransferase activity, at high (10^{-4} mol/l) concentration. Greater than 50% inhibition of MAO-A and MAO-B activity was later observed by Cott (1997) and Müller and coworkers (1998) when using extracts in the micromolar (10^{-6} mol/l) range. However, these investigators and others (Bladt and Wagner 1994; Cott 1995; Demisch et al. 1989) have emphasized that the effects of *Hypericum* on monoamine metabolism are not observed at clinically relevant, nanomolar (10^{-9} mol/l) concentrations. In vitro research also has demonstrated that *Hypericum* extract displays an affinity for 5-HT1, gamma-aminobutyric acid (GABA)-A, GABA-B, benzodiazepine, adenosine, and inositol triphosphate receptors in the micromolar (10^{-6} mol/l) range (Cott 1997). An affinity for muscarinic acetylcholine receptors also has been reported (Müller and Schäfer 1996). It should be noted once again that these findings were obtained using very high experimental concentrations, and that such concentrations are unlikely to be achieved when using a therapeutic dose of *Hypericum*.

At least one clinically utilized preparation (LI 160), a standardized *Hypericum* extract from Lichtwer Pharma, Germany, has consistently been shown to inhibit 5-HT, NE, and DA reuptake in vitro (Müller et al. 1997, 1998; Perovic and Müller 1995; Rolli et al. 1995). Interestingly, the LI 160 extract has recently been shown to inhibit the uptake of both 5-HT and NE in astrocytes, cells that surround synaptic terminals (Neary and Bu 1999). In this study, 5-HT transport was inhibited by 50%, whereas the affinity of NE for its uptake sites decreased 4.5-fold in the presence of *Hypericum*. Another recent study demonstrated inhibition of synaptosomal 5-HT uptake in the rat brain, but failed to reveal either an effect on 5-HT transport or a significant change in 5-HT levels following treatment with *Hypericum* (Gobbi et al. 1999). When taken together, the available in vitro data suggest a potential effect of *Hypericum* on central monoamine concentration, and indicate that the pharmacological mechanism of antidepressant action may be similar to that of conventional antidepressants, particularly SSRIs.

In animal experiments, *Hypericum* has been found to increase the level of several monoamines in the brain. In one investigation, the LI 160 extract was shown to induce a significant increase in 5-HT content in the rat cortex, but not in the diencephalon or brainstem (Calapai et al. 1999). In the same study, administration of LI 160 increased the level of NE and DA in the diencephalon (Calapai et al. 1999). Other researchers have reported that *Hypericum* is associated with increased levels of 5-HT in the rat hypothalamus and hippocampus (Yu 2000) and release of DA in the nucleus accumbens and striatum (Di Matteo et al. 2000).

Additional animal studies further illuminate the potential mode of antidepressant action associated with *Hypericum*. Research on rodents treated with *Hypericum* has corroborated behavioral effects frequently observed with traditional antidepressants. For example, *Hypericum* has been shown to improve performance in the learned helplessness test (Chatterjee et al. 1998a), chronic escape deficit model (Gambarana et al. 1999), and the forced swimming test (Bhattacharya et al. 1998; Butterweck et al. 1997, 1998; Chatterjee et al. 1998a, b; De Vry et al. 1999; Öztürk 1997). Further, the above animal studies have implicated serotonergic, noradrenergic, dopaminergic, and opioid system activity in the hypothesized mechanism of antidepressant action. Research on non-human, mammalian models also has revealed that chronic administration of *Hypericum* promotes adaptive changes in receptor function often observed during conventional antidepressant pharmacotherapy, including: (a) downregulation of cortical β-adrenoceptors without a change in receptor affinity (Müller et al. 1997), (b) upregulation of 5-HT1A postsynaptic receptors without a change in receptor affinity (Müller et al. 1997; Teufel-Mayer and Gleitz 1997), and (c) upregulation of 5-HT2 receptors (Müller et al. 1997). Most conventional antidepressants are known to downregulate the expression of both β-adrenoceptors and 5-HT2 postsynaptic receptors in the rat brain (Krishnan 1998; Leonard 1992; Peroutka and Snyder 1980; Sulser et al. 1978). Thus, the finding that *Hypericum* stimulates an upregulation in 5-HT2 receptor expression is in contrast to what is known about the action of TCAs or SSRIs. This response, however, does resemble the action of repeated electroconvulsive treatment on 5-HT2 receptor density, and suggests that improvement in serotonergic function may be due in part to enhanced 5-HT2 receptor expression (Müller et al. 1997; Nathan 1999).

According to quantitative electroencephalography, serotonergic (alpha), noradrenergic (theta), and cholinergic (delta) neurotransmission all appear to increase in both humans and rats treated with *Hypericum* (Dimpfel et al. 1999; Schellenberg et al. 1998). In addition, changes in EEG patterns indicative of relaxation and improved cognitive function have been observed in humans (Dimpfel et al. 1999; Johnson et al. 1994; Schulz and Jobert 1994) and rodents (Dimpfel and Schombert 1997; Dimpfel et al. 1998) treated with the extract. Another investigation examined the effect of *Hypericum* on sleep architecture in healthy humans (Sharpley et al. 1998). This study revealed that *Hypericum* significantly increases the latency to rapid eye movement sleep. This phenomenon has been demonstrated with nearly all conventional antidepressant drugs (Sharpley et al. 1998).

There is some indication that *Hypericum* may modulate certain neuroendocrine pathways. *Hypericum* has been shown to inhibit interleukin-6 (IL-6) expression, a cytokine that may stimulate the release of cortisol (Thiele et al. 1994). It is known that elevated endogenous cortisol is correlated with major depression (Felig et al. 1995), and though the evidence is unclear, it has been postulated that SSRIs may attenuate cortisol production via corticotropin-releasing factor antagonism (Valentino and Curtis 1991). It is possible that *Hyperi-*

cum-induced IL-6 inhibition might also underlie antidepressant activity by attenuating cortisol production. In contrast to this theory, one investigation has shown *increased* salivary cortisol levels in healthy male subjects following acute administration of LI 160 extract (Franklin et al. 1998). A second study by Franklin and coworkers failed to show an effect of *Hypericum* on plasma cortisol concentration, but did reveal a significant increase in growth hormone as well as a significant decrease in prolactin following a single oral dose (2700 mg) of LI 160 (Franklin et al. 1999). These authors suggested that *Hypericum* may activate dopaminergic pathways that are known to stimulate the release of growth hormone and the suppression of prolactin (Tuomisto and Mannisto 1985). A separate published report has revealed evidence that *Hypericum* can inhibit dopamine-β-hydroxylase (Kleber et al. 1999), an effect that could feasibly increase DA concentration in the central nervous system.

Collectively, the data reviewed suggest that therapeutic preparations of *Hypericum* extract appear to exert potentially significant pharmacological activity within several neurochemical systems believed to be implicated in the pathophysiology of depression. However, clinically relevant bioactivity associated with *Hypericum* remains to be clarified.

Isolated constituents

Hypericin

An early study found that a therapeutically relevant concentration of hypericin ($IC_{50}=10^{-5}$ mol/l) could irreversibly inhibit MAO-A and MAO-B activity in vitro (Suzuki et al. 1984). However, the sample of hypericin used in the above study was reportedly impure (Cott 1997), and the results of at least four more recent studies have revealed insignificant or no MAO inhibitor (MAOI) activity (Bladt and Wagner 1994; Cott 1995; Demisch et al. 1989; Müller et al. 1997). Due to lack of replication in both in vitro and ex vivo test systems, hypericin is not considered to act as an MAOI at clinically relevant concentrations (Blumenthal et al. 1998; Thiede and Walper 1994). Similarly, other recent studies demonstrate contradictory findings with regard to the effect of hypericin on monoamine uptake. One study found inhibition at very high ($IC_{50}=10^{-3}$ mol/l) concentrations (Müller and Schäfer 1996), two others found no effect (Müller et al. 1998; Rolli et al. 1995), and another study found that hypericin had no affinity for traditional monoamine receptors, nor an affinity for adrenergic, cholinergic, GABA, adenosine, or benzodiazepine receptors (Raffa 1998). The last study did find, however, that hypericin demonstrated a significant affinity for σ-opioid receptors.

Flavonoids

Flavonoid compounds contained in *Hypericum* are similar in chemical structure to synthetic MAOIs, such as toloxotone and brofaromine (Cracchiolo 1998). Indeed, the flavonoids quercetin, luteolin, and campferol have been shown to inhibit MAO activity in vitro (Thiede and Walper 1994; Upton et al. 1997). There is also in vitro evidence to suggest that some flavonoids, including hyperoside, quercitrin, isoquercitrin, and amentoflavone, may elicit a sedative effect that could involve both benzodiazepine and GABA receptor agonism (Baureithel et al. 1997; Cott 1997; Nielson et al. 1988). It has recently been postulated by one investigator that amentoflavone, a biflavonoid, may be the primary antidepressive constituent in *Hypericum* based on its potential GABA agonist effect (Cracchiolo 1998).

Similar to hypericin, the neurochemical activity associated with flavonoid constituents has been reported at relatively high experimental concentrations, uncharacteristic of what would be found in a clinically relevant extract of *Hypericum* (Thiede and Walper 1994). For instance, whereas synthetic antidepressant agents are known to reach a steady-state in human plasma in the nanomolar (10^{-9} mol/l) range (Potter et al. 1998; Tollefson and Rosenbaum 1998), most central activity associated with flavonoid compounds thus far has required an investigational preparation in the micromolar (10^{-6} mol/l) to millimolar (10^{-3} mol/l) range; a concentration range three to six orders of magnitude higher than that which would be expected to occur in human plasma following oral administration.

Xanthones

Although xanthones found in *Hypericum* appear to exhibit strong MAO-A and MAO-B inhibition in vitro (Suzuki et al. 1981), they are found primarily in the roots of the plant. The roots, however, are not currently included in the manufacturing process (ESCOP 1997). Therefore, it is presumed that xanthones do not account for *Hypericum*'s antidepressant bioactivity.

Hyperforin

Hyperforin, the most abundant lipophilic compound present in *Hypericum*, has shown much promise as a candidate constituent likely to account for this herb's antidepressant action. The following studies have demonstrated significant effects of hyperforin on serotonergic, noradrenergic, dopaminergic, cholinergic, and opioid system activity in vitro, as well as in animal models.

Chatterjee and colleagues (1996, 1998b) have demonstrated that pure hyperforin, as well as a hyperforin-enriched extract of *Hypericum*, can: (a) antagonize a variety of spasmogens in vitro, (b) antagonize 5-HT-induced ileum contractions, and (c) inhibit the uptake of 5-

HT in peritoneal cells. Further, these researchers reported that pure hyperforin in the micromolar (10^{-6} mol/l) concentration range inhibited the uptake of 5-HT, NE, DA, GABA, and the excitatory amino acid glutamate in synaptosomal preparations (Chatterjee et al. 1998a; Kaehler et al. 1999). A separate study by Müller and colleagues (1998) demonstrated that hyperforin in the nanomolar (10^{-9} mol/l) range has the ability not only to inhibit the reuptake of 5-HT, NE, and DA, but also to induce a downregulation in cortical β-adrenoceptor expression. According to Müller et al. (1998) and Nathan (1999), hyperforin is capable of inhibiting the reuptake of all three monoamines at a potency comparable to that of conventional 5-HT and NE inhibitors. Moreover, these authors note that the ability of hyperforin to inhibit the reuptake of 5-HT, NE, and DA at a nanomolar (10^{-9} mol/l) concentration sets it apart from any known antidepressant pharmaceutical. Though there is no clear evidence at present regarding specific neurotransmitter receptor inhibition, oral pretreatment of rats with pure hyperforin has been shown to inhibit a 5-HT-induced increase in heart rate, suggestive of serotonergic 5-HT3 receptor antagonism (Chatterjee et al. 1998b; Müller et al. 1998). Based on other recent experimental findings, some researchers expect that the molecular mode of antidepressant action for hyperforin is likely to be novel (Chatterjee et al. 1999; Gobbi et al. 1999; Singer et al. 1999) and may involve inhibition of 5-HT uptake by elevating intracellular Na^{+1} (Singer et al. 1999).

Hyperforin concentration recently has been correlated with antidepressant and anxiolytic-like activity in well-validated animal behavior models of depression (Bhattacharya et al. 1998; Chatterjee et al. 1998a, b). According to these authors, treatment with hyperforin was associated with improved resistance to stress in the forced swimming and learned helplessness tests. These tests are known to be useful in predicting antidepressant activity in humans. Moreover, extracts of *Hypericum* standardized for hyperforin content have been correlated in a dose-dependent manner with clinical antidepressive efficacy (Laakmann et al. 1998). Thus, there is cumulative evidence to suggest that hyperforin may be the key constituent responsible for *Hypericum*'s antidepressant property. Indeed, this particular compound may act in a way similar to that of conventional TCAs and SSRIs. If this is the case, future research should attempt to elucidate the bioactive nature of hyperforin in humans.

Toxicology

Adverse drug reactions (ADRs)

A European drug-monitoring study of 3250 patients revealed an overall ADR incidence of 2.4% for the clinical use of *Hypericum* extract in the treatment of depression (Woelk et al. 1994). The most commonly reported side effects were gastrointestinal irritations (0.6%), allergic reactions (0.5%), fatigue (0.4%), and restlessness (0.3%). A meta-analytic review concluded that when side effects do occur, they are generally mild, transient, and similar to placebo (Linde et al. 1996). Another recent review and meta-analysis of placebo- and drug-comparison trials revealed that the number of ADRs attributed to *Hypericum* varied according to the type of comparison medication, TCA or placebo. Interestingly, the incidence of ADRs associated with *Hypericum* was far greater in those RCTs that compared the herb to TCAs as opposed to inert, placebo medication; 33% vs 0.01% ADR incidence, respectively (Ernst et al. 1998). The most frequent ADRs reported in drug-comparison studies were gastrointestinal complaints, including nausea, abdominal pain, loss of appetite, and diarrhea (8.5%), dizziness/confusion (4.5%), fatigue/sedation (4.3%), dry mouth (4%), restlessness (2.6%), and headache (1.7%). The incidence of fatigue/sedation and dry mouth for comparison drugs (TCAs) was significantly higher at 20% each. Another recent investigation involving the use of LI 160 demonstrated an ADR frequency of 2% (Grube et al. 1997). To contextualize the above statistics, a recent review found the overall ADR incidence of several common SSRIs to be between 20% and 50% in most clinical trials, including the occurrence of more serious side effects such as cardiac arrhythmia, anorexia nervosa, and sexual dysfunction (Stokes and Holtz 1997).

A rare ADR that may be encountered with the use of *Hypericum* at high or very high doses, is photosensitization (Blumenthal et al. 1998; ESCOP 1997). Symptoms indicative of phototoxicity include dermal erythema, rash, and pruritis. According to one recent RCT involving the standardized extract LI 160, there does not appear to be a correlation between total plasma hypericin concentration and photosensitivity in humans (Brockmöller et al. 1997). However, this study did find a slight but statistically significant increase in dermal sensitivity to selective ultraviolet-A (UV-A) irradiation following a single oral dose of 3600 mg (four times the recommended daily dose). In addition, the study revealed a statistically significant but marginal increase in dermal sensitivity to both solar simulated irradiation and selective UV-A light following 15 days of treatment with high-dose *Hypericum* (1800 mg/day, twice the normal recommended daily dose). This increase in dermal light sensitivity was evidenced by a change in skin pigmentation, and could be compensated by reducing light exposure time 21%. Though these artificial experimental conditions do not represent normal ambient settings, the authors concluded that phototoxic reactions may occur at plasma hypericin concentrations above 100 µg/l or, alternatively, when pure hypericin is ingested as opposed to a whole plant extract.

Another recent investigation of LI 160 demonstrated that following both a single oral dose (1800 mg) and steady-state administration (900 mg/day for 7 days), peak hypericin levels found in skin blister fluid were at least 20 times below the estimated phototoxic concentration of 100 µg/l (Schempp et al. 1999). Similarly, a study

conducted on the phototoxic effect of *Hypericum* extract on human keratinocytes concluded that plasma hypericin levels expected during anti-depressive therapy are far too low to induce phototoxic skin reactions (Bernd 1999).

Nevertheless, there has been one recent report of *Hypericum*-induced subacute toxic neuropathy in a 35-year-old female following prolonged exposure to sunlight (Bove 1998). This case is the first published report of phototoxicity associated with a therapeutic dose of *Hypericum* (500 mg/day). One previous report of mild, reversible dermal phototoxicity in humans was observed in a study in which high-dose synthetic hypericin (35 mg) was delivered intravenously as an experimental antiviral therapy (James 1992). The dosage in the latter study was over 30 times the recommended daily dose of hypericin for the treatment of depression (Blumenthal et al. 1998).

Two potential cases of induced mania recently have been reported in bipolar patients taking 900 mg *Hypericum* extract daily (Nierenberg et al. 1999). Based on their clinical observations, these authors concluded that physicians should screen for hypomania or mania prior to recommending the use of *Hypericum* in the treatment of depression. It was noted, however, that manic episodes could simply have been due to the natural cycle of bipolar disorder. Thus, it remains unknown as to what extent *Hypericum* may influence the course of manic depression.

Herb–drug interactions

Three authoritative reference publications on herbal medicine currently report little to no data on herb–drug interactions (Blumenthal et al. 1998; ESCOP 1997; PDR for Herbal Medicines 1998). This is primarily due to the paucity of drug interaction data available for *Hypericum*. Empirical data must be obtained to better establish the safety of this herbal product. As discussed below, research is now beginning to accumulate in this area.

One placebo-controlled trial that investigated the effect of *Hypericum* on blood alcohol concentration found no effect, as well as no change in cognitive-motor performance, in healthy volunteers (Schmidt et al. 1993). Three independent animal studies have demonstrated that *Hypericum* is associated with reduced alcohol intake in alcohol-preferring rats (De Vry et al. 1999; Perfumi et al. 1999; Rezvani et al. 1999). Perfumi and colleagues further reported that *Hypericum* did not affect blood-alcohol levels, and that reduced alcohol intake was not related to changes in the pharmacokinetics of ethanol. Taken together, these data suggest that *Hypericum* does not interact pharmacologically with ethanol.

It recently has been hypothesized that *Hypericum* extract may interfere with anesthetic drugs (Koupparis 2000). However, this hypothesis is based on the assumption that hypericin exhibits clinically significant MAOI activity, an effect which is *not* supported by the current scientific literature. To date, there are no published reports of interaction between *Hypericum* and anesthetic drugs.

Data on single dose toxicity, reproductive toxicity, carcinogenicity, and long-term safety of *Hypericum* are extremely limited. Some animal data appear to indicate low toxicity for the herb. For example, no significant tissue lesions nor any adverse effects on the liver were observed in rats fed *Hypericum* as 5% of their diet for 119 days (Garrett et al. 1982). However, in this study it was reported that *Hypericum* induced hepatic enzyme activity. This effect could potentially increase metabolism and thus decrease the bioavailability of drugs that are normally broken down in the liver. Indeed, several recent reports in humans have indicated that *Hypericum* may function as a potent inducer of hepatic enzymes. Ernst (1999) reported that *Hypericum* extracts may roughly double the metabolic activity of hepatic cytochrome P-450 (CYP). Further, Ernst (1999) noted that according to eight reported cases of potential *Hypericum*–drug interactions, plasma concentrations of the concomitant medication was reduced. Comedications included theophylline, cyclosporine, warfarin, and ethinylestradiol/desogestrel, each of which is metabolized by hepatic CYP microsomal oxidase enzymes. This phenomenon is supported by other recent findings in which *Hypericum* extract significantly decreased the plasma concentration of digoxin (Johne et al. 1999), phenprocoumon (Maurer et al. 1999), and the HIV-1 protease inhibitor indinavir (Piscitelli et al. 2000). Other researchers have recently reported that a reagent-grade *Hypericum* extract significantly induces CYP3A4 isozyme activity in healthy human subjects following a 14-day treatment period at the recommended therapeutic dosage of 900 mg/day (Roby et al. 2000). In their paper, Roby and colleagues (2000) noted that CYP3A4 "is responsible for the metabolism of more than 73 medications and numerous endogenous compounds", including protease inhibitors, nonsedating antihistamines, calcium channel blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, benzodiazepines, estrogens, macrolide antibiotics, cyclosporine, carbamazepine, ketoconazole, and cortisone. These authors confirmed the possibility that *Hypericum* may effectively reduce the plasma concentration of such CYP3A4 substrate medications if hepatic metabolism is induced to a clinically significant degree. On the contrary, another recent investigation has demonstrated no significant effect on CYP3A4 or 2D6 activity in healthy volunteers who were administered *Hypericum* concomitantly with alprazolam or dextromethorphan (Markowitz et al. 2000). In comparison to the inducing effect of *Hypericum* on CYP isoenzyme activity, it is known that certain SSRIs, such as fluoxetine and sertraline, inhibit the activity of CYP2D6, which can increase the concentration of certain pharmaceuticals taken concurrently (Crewe et al. 1992). Overall, the data available on hepatic metabolism and potential drug interactions raise legitimate concerns regarding the possibility that *Hypericum* ingested during pharmacotherapy may result in accelerated elimination of the conventional pharmaceutical agent.

There has been one published report of five possible cases of central serotonin syndrome in elderly patients treated simultaneously with *Hypericum* and an SSRI (Lantz et al. 1999). Serotonin syndrome can be attributed to an overactivation of central serotonin receptors, and may manifest with features including abdominal pain, diarrhea, sweating, fever, tachycardia, elevated blood pressure, altered mental state (for example, delirium), increased motor activity, irritability, hostility, and mood change (Tollefson and Rosenbaum 1998). This phenomenon is particularly dangerous in older individuals (Ernst 1999). Therefore, special consideration should be given when administering *Hypericum* extract for the treatment of depression in this particularly sensitive patient population.

Recent toxicological work performed with LI 160 found the no-effect single dose to be above 5000 mg/kg in mice and rats (Leuschner 1996). Chronic toxicity studies involving both rats and dogs revealed only nonspecific symptoms of toxicity, including weight loss, minor pathological changes in the liver and kidneys, and some cellular changes in the adrenal glands (Leuschner 1996). In addition, no effect on fertility or reproduction was found, nor was any mutagenic potential observed. Earlier research also demonstrated an absence of mutagenic potential in all in vivo and most in vitro test systems (Okpanyi et al. 1990; Poginsky et al. 1988). Two recent findings have reported inhibited sperm motility, compromised sperm viability, lower penetration of oocytes, and sperm DNA denaturation in hamsters (Ondrizek et al. 1999a, b). Unfortunately, the specific contents of the *Hypericum* preparation used by Ondrizek and coworkers were not disclosed, and the experimental concentrations were several orders of magnitude higher than what is currently considered a therapeutically relevant dosage. Therefore, the reported possible effects on sperm viability must be interpreted with caution.

Concern has been raised regarding the possibility that some women may use *Hypericum* in place of standard antidepressant medication during pregnancy, as the herb may be perceived as a safe and natural alternative (Grush et al. 1998). Grush and her colleagues cited two cases in which women initiated *Hypericum* treatment during pregnancy without medical consultation. In one instance, a woman discontinued an effective pharmacological treatment regimen, placing herself at risk for relapse of refractory depression. Grush et al. (1998) cautioned against the use of *Hypericum* during pregnancy due to a lack of evidence for both efficacy and reproductive safety.

In sum, there are few well-characterized data available on the toxicological and pharmacological profile of *Hypericum* in animals, and such data are just beginning to be obtained in humans. Considering the lack of data available on teratogenicity, mutagenicity, and other potentially harmful effects that may occur during pregnancy and subsequent lactation, use of *Hypericum* by women who are pregnant or nursing, or by those women who may become pregnant, must be considered with caution. Similarly, caution is warranted to those patients who are either elderly and/or currently being treated with one or more pharmaceutical drugs.

Pharmacokinetics

Pharmacokinetic studies in humans have revealed that clinically relevant dosages of total hypericin (approximately 1 mg/day) reach a maximal plasma concentration in the nanomolar to micromolar range after 4–6 h, and achieve a steady-state after about 4 days (Brockmöller et al. 1997; Kerb et al. 1996; Staffeldt et al. 1994; Upton et al. 1997). The absorptive lag-time is roughly twice as long for hypericin (approximately 2 h) versus pseudohypericin (approximately 1 h), and elimination of both compounds is reported to be slow; approximately 25 and 40 h, respectively (Staffeldt et al. 1994). In another recent investigation of an extract containing 300 mg *Hypericum* (14.8 mg hyperforin), hyperforin was shown to reach a maximal plasma concentration of 150 µg/l (280 nM) after 3.5 h (Biber et al. 1998). Half-life and elimination times for hyperforin were 9 and 12 h, respectively. Though no accumulation of hyperforin in plasma was observed in a repeated-dose study, the estimated steady-state plasma concentration following a normal therapeutic regimen was approximately 100 µg/l (approximately 180 nM); a concentration similar in magnitude to the SSRIs fluoxetine, paroxetine, and fluvoxamine (Biber et al. 1998).

Despite research efforts to date, therapeutic brain concentration remains a critical, unanswered question. It has been postulated that the concentration of hypericin in the brain may reach only 5% of that measurable in plasma, yet the half-life of hypericin in brain tissue could be in the order of weeks (Upton et al. 1997). Pharmacokinetic factors associated with *Hypericum* extracts, such as bioavailability (15–20%), poor blood–brain barrier penetration, and slow elimination time, do seem to correlate with the 4–6 week treatment period typically required to achieve a therapeutic benefit in patients (Bennett et al. 1998). Further, based on the known anti-cholinergic side effect profile of several conventional antidepressant drugs, it has been suggested that similar pharmacological activity may indicate attainment of therapeutic efficacy when using *Hypericum* (Bennett et al. 1998). According to this theory, the half-maximal inhibitory concentration of *Hypericum* at acetylcholine receptors (for example, IC_{50}=1%) could represent the concentration necessary to elicit an antidepressive effect. However, due to the low occurrence of adverse effects associated with *Hypericum*, including anti-cholinergic side effects, the search for a valid pharmacological indicator of therapeutic efficacy continues.

Summary

Clinical outcome research thus far suggests a possible role for *Hypericum* in the treatment of depression. Nu-

merous in vitro studies, as well as available preclinical and clinical data, indicate potential effects of *Hypericum* extract on human neurotransmission. However, the extent to which *Hypericum* produces clinically significant changes in neurochemistry remains to be determined. Presently, the antidepressant bioactivity of *Hypericum* is not established. Given what is known of its mechanism of action, *Hypericum* may have pharmacological properties similar to conventional antidepressants, namely TCAs and SSRIs. Based on its pharmacodynamics, there are also potentially hazardous effects when combining *Hypericum* with SSRIs and/or those pharmaceuticals metabolized by the hepatic CYP3A4 enzyme. Furthermore, *Hypericum* affects 5-HT2 receptor expression and DA neurotransmission in ways that are not characteristic of traditional antidepressants. Additional pharmacological and biochemical research on *Hypericum* and its many bioactive constituents is required before definitive conclusions can be reached regarding the underlying mechanism of antidepressant action. That notwithstanding, the cumulative body of evidence to date indicates that *Hypericum* may exert a significant influence on catecholamine and other neurochemical systems believed to be implicated in the etiology of depression. Additional in vivo research is needed to confirm whether or not therapeutic preparations of *Hypericum* are capable of affecting monoamine (5-HT, NE, DA) concentration via synaptic reuptake inhibition and/or regulation of serotonergic or β-adrenoceptor expression or sensitivity. Current theory suggests that the elusive antidepressant mechanism in question likely falls within one of three domains: (1) similar in nature to current synthetic antidepressant activity, (2) the product of synergistic interactions involving multiple bioactive constituents across neurochemical systems, and/or (3) an unknown mechanism yet to be determined (Bennett et al. 1998).

Convergent evidence from in vitro, animal, and human research has demonstrated significant change or improvement in serotonergic, noradrenergic, dopaminergic, GABA, and opioid system functioning; effects that parallel to some degree the pharmacological action of TCAs and SSRIs. In addition, there is some evidence to suggest that *Hypericum* may possess a novel capability to both inhibit DA reuptake and upregulate 5-HT2 receptor expression in living organisms. In the absence of well-replicated data concerning specific central activity in humans, hypotheses regarding a pharmacological relationship between *Hypericum* and conventional antidepressants must remain speculative at this time. In summary, given what is currently known and unknown about the biological properties of *Hypericum*, caution is warranted to those who use this herbal extract.

Product standardization and regulatory status

Of immediate concern to the physician and patient alike is the reliability of herbal products sold in the United States. Presently classified as dietary supplements (i.e., food) by the U.S. Food and Drug Administration (FDA), herbal remedies are not subject to the extensive preclinical and clinical trials pharmaceutical drugs must undergo in order to demonstrate safety and efficacy. Based on the present classification scheme, manufacturers of herbal remedies are permitted to make health claims on product labels if such claims are related to body structure or function. However, these statements may mislead consumers if not made responsibly. For this reason, dietary supplements including herbal preparations must include the following disclaimer: "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Despite their current classification, it is clear that herbal remedies such as *Hypericum are* used as drugs by a significant proportion of the U.S. population to treat common illnesses and symptoms of disease (Astin 1998; Eisenberg et al. 1998; Fugh-Berman and Cott 1999; Yager et al. 1999). The ramifications of classifying herbs as dietary supplements in the U.S. are many, and include valid concerns such as: (a) the reliability of product standardization within the botanical industry (i.e., purity, potency, side effect profile), (b) the scientific basis of clinical practice when incorporating herbal medicines, and (c) implications for consistent treatment and therapeutic regimens that may involve herbs.

At present, U.S. manufacturers of herbal products are responsible for self-monitoring industry practices. Some manufacturers have sought and obtained United States Pharmacopoeia (USP) recognition for consistent product purity and potency; many, on the other hand, have not. USP approval represents an appreciable means of external quality assurance, though adherence to USP standards is completely voluntary. As monographs for herbal preparations are added to the National Formulary, manufacturers of botanical products have the opportunity to adhere to USP specifications of product identity, strength, quality, purity, packaging, and labeling. In fact, a standard monograph for St. John's wort has recently been added to the National Formulary, thereby allowing select products to include the "USP" seal on their label as an assurance of quality for consumers (USP 1999).

In several European countries, regulation of herbal products is more stringent. For instance, the German Commission E is responsible for regulatory approval of herbal medicines in Germany. This governmental body, somewhat analogous to the FDA, recommends the use of botanicals as drugs based on extensive expert reviews of preclinical and clinical data regarding medicinal safety and efficacy. Many herbal products that have received German Commission E approval are now available to pharmacies and physicians in the U.S. However, until herbal products in the U.S. are regulated by either a governmental or non-governmental body, the patient, as well as the practicing physician, cannot be assured of the purity, potency, or safety profile of a given compound, unlike those agents that are subject to review by the FDA. Many herbal products such as *Hypericum* exhibit significant patterns of pharmacological activity that may hold

promise for effective treatment of various illnesses, including depression. Therefore, tightly regulated botanical preparations would benefit not only patient care, but future scientific investigations as well.

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