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ST. JOHN'S WORT

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ABSTRACT

Objective: The objective of this article is to review the current knowledge of the pharmacology, sites of action, and therapeutic effectiveness of St. John's Wort. *Method:* The method used was a review of the available literature, using keywords to search the medline database. Bibliographies of the papers, thus obtained, were searched for further documents not referenced by medline. We reviewed papers from this collection. *Results:* This review reveals that most of the available data on efficacy and safety of St. John's Wort involve its use in mild to moderate depression. Much, but not all of the prevailing opinion is positive. Nevertheless, the quality of therapeutic trials vary so greatly that definitive conclusions are not possible. Both the source and mode of St. John's Wort's therapeutic effect are unclear. We need further controlled studies of effectiveness, safety, and mode of action. In addition to its use in depression, there are reports suggesting possible therapeutic effects in other conditions such as certain malignancies and infections, but these are far too preliminary to permit any conclusions.

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Key Words: hypericum; antidepressive agents; plants, medicinal

INTRODUCTION

As the twenty-first century begins, more patients in the United States are turning to alternative or complimentary medical treatments. Forty percent of respondents to a recent survey used some form of alternative medicine [1]. The yearly value of alternative medicine remedies in the United States was estimated at 217 billion dollars in 1997 [2]. In this growing movement toward "natural" treatments, extract of St. John's Wort, Hypericum perforatum, has become increasingly popular as a remedy for depression. A survey revealed several themes in the decision to use St. John's Wort. These included personal health care values favoring use of alternative treatments, belief in the purity and safety of such products, willingness to try new things, need to control medical care, definite depressive symptoms, self-perception of the depression as mild, and relative inaccessibility of the medical care and mental health care systems [3]. Given the trend for patients to explore unconventional treatments, physicians should be aware of what is known about St. John's Wort, including its potential risks and benefits.

HISTORICAL BACKGROUND

Hypericum perforatum is a small shrub, one of a genus widely distributed throughout temperate regions. The bright, yellow flowers appear in midsummer, about the time of St. John the Baptist's day, June 24th, which may have given the plant its common name. The flowers are attractive enough for decorative use in gardens, but the plant's invasive nature also qualifies it as a weed. The leaves and flower buds are rich in complex aromatic compounds, some of which take on a bright red color when exposed to light. St. John's Wort has a long history as a remedy. It was cited in antiquity by Dioscorides [4]. Neither Turner [4] in the sixteenth, nor Gerarde [5] in the seventeenth century, mentioned its use in depression, but rather, recommended it for sciatica, ague, as a vulnerary for wounds, to "stop bleedings, provoke urine, heal ulcers, and cure burnes." However, Culpeper [6] in 1652, found it useful "for worms, melancholy and madness (sic)." In the mid-twentieth century, plant leaves and extracts became commercially available and widely prescribed by physicians in Europe. In 1984, the German Commission E monograph [7] recommended using the herb as a tea for "psychogenic disturbances, depressive states, anxiety, and/or nervous excitement." The Lawrence Review of Natural Products mentions its use in anxiety and depression [8]. In the United States, preparations of St. John's Wort are now ubiquitous on store shelves. The herb is the subject of such popular books as *Hypericum and Depression* [9] and *The Natural Prozac Program* [10], with the latter awarding

it the unsubstantiated encomium: "St. John's Wort beats Prozac hands down." Hypericum even has its own Web site on the internet.[1]

Those using St. John's Wort in the desire for uncomplicated, natural remedies may be surprised to find that it is neither uncomplicated nor simple. There are numerous species of Hypericum with different proportions of active constituents [11]. Difficulty in identification was demonstrated recently when, after printing a picture of St. John's Wort to accompany an article on the subject, the British Medical Journal received a tart letter to the editor from a botanist insisting that the plant depicted had been misidentified [12]. The character of the medicinal preparation is affected by variation in season and method of harvesting, presence of adulterants, parts of the plant used, and techniques of extraction [11, 13]. In Europe, governmental agencies license and standardize preparations of St. John's Wort by assay of Hypericin content [13]: Unfortunately, consumers in the United States have no assurances of potency or purity of herbal products, which are regarded here as dietary supplements rather than drugs. Impurities, mislabeling, toxic adulterants, interactions with other medications are not uncommon in these products [14].

METHODS

The authors conducted an all-language search of the medline database for the years 1967-1999 using the key words "Hypericum, and exp herbal medicines" or "exp antidepressive agents." We searched the bibliographies of the papers thus obtained for any papers not cited in medline. The publications were classified into basic neuropharmacology, clinical studies, and reviews. Reports of most uncontrolled, observational clinical studies were discarded as were most opinion papers. Twenty-two clinical studies were, where necessary, translated and reviewed by two or more of the authors. Six papers were discarded because they lacked double blind controls. The basic science reports were reviewed by one or more of the authors. We did not do meta-analysis of the clinical studies as we felt the papers differed so greatly as to make analysis difficult. We did not wish to take the course of one previous review, which culled the literature down to six papers. Two of the three authors (HLF, DAM, EJSK) reviewed and discussed all of the clinical papers. Two of the authors (HLF, JMG) reviewed the pharmacology papers.

CLINICAL STUDIES OF HYPERICUM IN DEPRESSION

Anecdotal reports of Hypericum's antidepressant activity led psychiatrists in Europe to seek more thorough exploration of safety, physiologic effects, and

[1] HTTP://www.hypericum.com

antidepressant efficacy. Single and double blind studies followed the first anecdotal reports. There are now several dozen clinical research reports, several reviews, and five surveys of controlled studies of Hypericum in depression. In 1994, Harrer and Schulz [15] reviewed twenty-five papers; in 1995, Ernst [16] reviewed twelve; in 1996, Linde et al. [17] reviewed twenty-three; in 1997, Volz [18] reviewed fifteen papers; and in 1999 Kim, Streltzer, and Goebert [19] reviewed six papers. These reviews covered many of the same papers. The review of Linde et al. included a meta-analysis of pooled results of 1757 patients treated in twenty-three studies, reporting that the Hypericum cohort had a significantly better outcome than placebo, and that Hypericum effectiveness was equal to that of the index tricyclic or tetracyclic antidepressants. Kim, Streltzer, and Goebert attempted to increase the validity of their meta-analysis by restricting the papers analyzed to studies using randomized, double blind comparisons, on defined subjects, using most recent diagnostic systems (ICD-10 or DSM IIIR, IV), with quantified accession and outcome measures using the Hamilton depression scale (HAMD). Only six of the papers surveyed met these stringent criteria. Their meta-analysis revealed fewer side effects, but improvement only 1.5 times more likely with Hypericum than comparison cohorts. Thus far clinical studies have been performed in Europe. Sizes of the patient population varied from fourteen to 209; the dose of Hypericum extract varied from 300 to 1800 mg per day; ten of the studies cited in Table 1 used Hypericum-Praparat LI 160 containing 300 mg of Hypericum extract [20-29], four of the studies used a standardized hydro-alcoholic liquid [30-33], and one used a research preparation standardized for hyperforin content [34]. The duration of treatment varied from four to twelve weeks; research was performed in a single or multiple sites; and the majority of patients met either Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for adjustment disorder with depressed mood or dysthymic disorder, or International Classification of Diseases (ICD) diagnosis of neurotic depression. The Hamilton depression scale (HAMD) was used to evaluate severity of depression in many of the studies. Scores at intake in those reports using this instrument varied from 13 to 25; thus, with few exceptions the depressions studied were of mild to moderate severity according to established cutoff scores [35]. Several authors who gave ranges did not include average scores at intake. Only one study reported on outcome in severe major depressive disorder with an intake HAMD average score of 25 [29]. Another reported on "moderately severe" neurotic depression with intake HAMD scores of 16 to 20 [36]. In addition to the Hamilton depression scale (HAMD), severity and outcome measures in these studies included von Zerssen's health complaint (DL) and depressivity indices (DS), and the Clinical Global Impressions scale (CGI). Comparison drugs included imipramine, amitriptylline, maprotoline, and several benzodiazepine drugs. Many of these papers reported positive results: improvements greater than placebo or equal to comparison drugs, with less side effects. Table 1 contains a summary of the outcomes and characteristics of some of the investigations

focusing on outcome using Hypericum extract in depressive disorders compared to other antidepressant medications or placebo.

DISCUSSION

These studies have been criticized. The patients treated were less severely depressed than those usually entered into drug trials, with entering HAMD scores as low as 13 in one study [37]. Some papers were criticized for lack of diagnostic specificity; major depression was not always separated from bipolar or adjustment disorders. There was unusually low response rate in the placebo group. Some of those comparing Hypericum to standard medication often used smaller than customary doses of antidepressants in control patients [38]. The only study reporting comparison to an adequate dosage of tricyclic (Desipramine 150 mg), did not give clear therapeutic advantage to Hypericum. Although more are expected, we were able to find only one published report comparing St. John's Wort to an SSRI antidepressant [39]. Workers in this area tended to publish multiple papers using the same data. Not all of the instruments used in evaluation are familiar to the American reader. In those studies using the Hamilton, training and experience of the raters was not discussed. In two studies reporting successful outcome, the preparation studied combined Hypericum with Valerian extract, an herbal with psychotropic properties of its own [40, 41]. Another botanical (Neurapas) reported to be effective in a double blind study contained Hypericum, Valerian, corydalis, and Papaver californicum (California poppy), which obscured which of the ingredients were responsible for the therapeutic effect [42]. The duration of the depressions and number of prior episodes were not explicated. The length of the trials usually did not exceed six weeks and no long-term follow-ups were given.

The contrast between the lavish praise of the popular press and methodological shortcomings in the literature led one group of reviewers to conclude that St. John's Wort should not be used "until more definitive data are available" [43]. In considering these criticisms, one must note that the philosophy of drug trials in Europe differs a bit from that in the United States; perhaps less removed from the realities of daily practice.

Studies utilize multiple centers and researchers, each with relatively small numbers of subjects. Physicians in the employ of the manufacturer feel comfortable performing the clinical studies themselves. Also, the smaller doses of comparison antidepressants criticized in these studies are customary in Europe. Furthermore, the controls for duration of illness and number of prior episodes, lengthy trials, and prolonged follow-ups are unusual in traditional drug trials.

In a different type of evaluation, Woelk, Burkard, and Grünwald [44] tabulated the results of drug monitoring reports on 3250 patients. These thorough reports are required from all treating physicians in Germany by the German Food and Drug

Table 1. Double Blind Efficacy Studies Comparing Hypericum to Tricyclic Antidepressants or Placebo

Author and Year	Duration (wks)	Number	Diagnoses	Test Instruments	Intake Severity	Control	Results
Hoffman 79 [30]	6	60	Miscellaneous depression	52 item symptom rating	"Mild"	Placebo	Favored Hypericum
Halama 91 [20]	4	50	Neurotic depression, brief reactive depression	HAMD, CGI, BLs	HAMD 16-20	Placebo	Favored Hypericum
Harrer 91 [31]*	6	120	Neurotic depression, brief reactive depression	HAMD, HAMA, DS	HAMD 16-20	Placebo	No difference in outcome
Reh 92 [37]	8	50	Neurotic depression, brief reactive depression	HAMD, HAMA, DS, CGI	HAMD 13-25	Placebo	Favored Hypericum
Osterheider 92 [32]	8	46	"Endogenous" depression	HAMD, CGI, BDI, HAMA	not stated	Placebo	Favored Hypericum
Quandt 93 [33]	4	88	Neurotic depression	HAMD	HAMD > 15	Placebo	Favored Hypericum
Lehrl 93 [21]	4	50	Neurotic depression, brief reactive depression	HAMD, HAMA, SB-S, CGI, KAII, cognitive tests	HMD 16-26	Placebo	No significant difference on HAMD
Schmidt 93 [22]	6	65	Neurotic depression	HAMD	HAMD 16-20	Placebo	Favored Hypericum
Bergmann 93 [91]	6	80	Mild major depression, moderate major depression	HAMD	Average HAMD = 15.5	Amitriptyline 30 mg	Favored Hypericum

Hübner 94 [23]	4	39	Neurotic depression, brief reactive depression	HAMD, CGI, BL	not stated	Placebo	Favored Hypericum
Harrer 94 [24]	4	102	Severe major depression	HAMD, DS, CGI	HAMD > 16	Maprotiline 75 mg	No difference in outcome
Sommer 94 [25]	4	105	Neurotic depression, brief reactive depression	HAMD	“Mild¨	Placebo	Favored Hypericum
Vorbach 95 [26]	6	135	Major depression	HAND, CGI, DS	not stated	Imipramine 75 mg	No difference in outcome
Hänsgen 94 [27]	6	72	Major depression	HAMD, DS, CGI, BEB	HAMD > 15	Placebo	Favored Hypericum
Wheatley 97 [28]	6	15	Major depression	HAMD, CGI, MADRS	HAMD 17-24	Amitriptyline 75 mg	Amitriptyline slightly better on some measures
Vorbach 97 [29]	6	209	Severe major depression	HAMD, DS, CGI	ICD10:F33.2	Imipramine 150 mg	No difference in outcome
Laakman 98 [34]	6	147	Major depression	HAMD, DS, CGI	HAMD > 16	Placebo	Favored Hypercium

Montgomery-Asberg Rating Scale for Depression = MADRS
Clinical Clobal Impression Scale = CGI
Hamilton Depression Scale = HAMD
von Zersen’s Health complaints = BL
Symptom evaluation Questionnaire = BEB
von Zersen’s Depression Scale = DS
Hamilton anxiety scale = HAMA
Beck Depression Index = BDI
neurotic depression = ICD(300. 4, brief depressive reaction = ICD9 309, major depression = DSM 296. xx, mild major depression = F32. 0, moderate major depression = ICD10 F32. 1, severe major depression = ICD 10 F32.2, F33. 2

act. The responses indicated that 30 percent of the reported cases "improved or normalized," a rather unimpressive therapeutic effect.

In related research, Hypericum is reported to be as effective as phototherapy in treatment of seasonal affective disorders [45, 46]. Hypericum has been evaluated in "climacteric" depressions [47] and in thirty surgical patients who became depressed after being informed of the need for an amputation [48]. Other workers have studied the effects of Hypericum on sleep architecture [49], and report that Hypericum extract increased time in deep sleep stages in older volunteers without increasing the total sleep time.

SIDE EFFECTS

Reported side effects have been mild. A drug monitoring study reported the total incidence of side effects as 2.4 percent [44]. In all of the studies comparing Hypericum with standard tricyclic antidepressants, Hypericum had fewer side effects. Gastrointestinal complaints are the most common; allergic reactions, fatigue, and anxiety also occur. The issue of photosensitivity is undecided. Studies suggest no appreciable photosensitivity in humans at plasma concentrations ordinarily reached in clinical usage [50, 51]. Nevertheless, the German monograph suggests possible photosensitivity reactions [7], there are case reports of photosensitization in those taking St. John's Wort [52], and dermal photosensitivity has been reported in HIV-positive patients receiving extremely high-dose hypericin (35 mg per day intravenously) as an experimental antiviral therapy [53]. Hypericum has no deleterious effect on cognition and memory [21]. There is no evidence of cardiac toxicity [54]. The most recent area of concern about Hypericum involves its effects on sperm motility and possible damage to genetic material. High concentrations of Hypericum extract decreases sperm motility and viability [55] and appear to cause mutation of genetic material [56]. The clinical significance of this is not clear. Mutagenesis of somatic cells in embryonic mammals did not occur [57].

Drug interactions are being reported with increasing frequency. There have been recent reports that Hypericum lowers blood levels of digoxin [58]. A recent review cited case reports of lowered levels of theophyline, cyclosporine, warfarin, estrogens, probably due to enzyme induction [59]. The authors expect more instances of such drug interactions in the future. The alleged effects of Hypericum in MAO inhibition have led to concern that the herb, used in combinations with serotinergic antidepressants might precipitate a serotonin syndrome. Only a handful of reports of serotonin syndrome due to drug interactions have appeared despite the millions of doses of Hypericum given [60]. A case of toxicity resulting from interaction between use of Hypericum and an SSRI reported excessive sedation from Hypericum extract in combination with paroxetine [61]. There is one report of mania in a patient taking Hypericum [62], and a report of acute delirium associated with a combination of Hypericum, Valerian, and loperimide [63].

ACTION OF ST. JOHN'S WORT

St. John's wort has complex neuropharmacologic activity. In vitro experimentation with crude Hypericum extract revealed many effects on neurotransmission, including: 1) inhibition of MAO-A, MAO-B, and catechol-O-methyltransferase [64, 65], 2) neurotransmitter receptor binding at 5-HT, NE, GABA, benzodiazepine, adenosine, inositol triphosphate (IP3), and muscarinic (mAChR) receptors [65, 66], and 3) neurotransmitter reuptake inhibition of serotonin, norepinephrine and dopamine [67-72]. Hypericum suppresses PHA (phytohemagglutinin)-stimulated release of interleukin-6 (IL-6) [73], it decreases serotonin receptor activity over the short term in vitro [74], but up-regulates serotonin receptors in vivo over the long term [75].

St. John's wort contains at least ten groups of biologically active compounds. Three of these, the napthtodianthrones, flavinol glycocides, and phloroglucinols, have central nervous system activity [13]. The naphthodianthrones include hypericin, which until recently was considered responsible for the anti-depressant effects of St. John's Wort. Flavonol glycosides contained in St. John's Wort include quercitin, hyperoside, quercitrin, isoquercitrin, rutin, luteolin, and campferol, as well as biflavonoids such as amentoflavone. Phloroglucinol compounds, namely hyperforin and adhyperforin, are important constituents of the herb. Other groups appear to have no antidepressant activity.

The effort to delineate which of these compounds produce therapeutic activity has proceeded slowly because of the complexity of the materials involved [76]. At first hypericin inhibition of monoamine oxidase (MAO) activity in isolated rat brain homogenates was felt to account for anti-depressant activity associated with St. John's Wort [77]. Subsequent experimentation revealed only very slight MAOI activity at concentrations well above therapeutic levels [78], and hypericin is no longer considered a clinically significant monoamine oxidase inhibitor [64, 79].

Flavonol glycocides have also been shown to inhibit MAO activity in vitro, but also have little effect at levels likely to be encountered in treatment [64, 80]. There is in vitro evidence to suggest that the flavonoids have affinity for GABA receptors which may account for St. John's Wort's mildly sedative effects [65, 81, 82].

Hyperforin, the most abundant lipophilic compound present in St. John's Wort, is currently the best candidate for the source of anti-depressant action. Several studies to date have demonstrated significant effects of hyperforin on serotonergic, noradrenergic, dopaminergic, cholinergic, and opioid system activity in vitro. Hyperforin has exhibited anti-depressant and anxiolytic activity in animal behavior models [83, 84]. Furthermore, extracts of St. John's Wort standardized for hyperforin content have been correlated in a dose-dependent manner with clinical anti-depressive efficacy in human studies [34]. Clearly, additional research on Hypericum and its many active constituents is needed before definitive conclusions can be reached regarding the underlying mechanism of anti-depressant action in humans (see Table 2).

Table 2. Central Pharmacologic and Biochemical Activity Associated with St. John's Wort and Its Bioactive Constituents

Biochemical Class	Constituent(s)	Enzymatic Effect(s)	Central (CNS) Activity	Receptor Binding	Uptake Inhibition	Experimental Concentration Range
Crude Extract (e.g., LI 160)	10+ bioactive constituents	MAO inh., COMT inh. [64, 65]	5-HT, NE, DA, GABA, Ach [65, 66]	5-HT, MAO, GABA, NE, Benzo, IP3, Adenosine, mAChR [65, 66]	5-HT, NE, DA [67-70]	0.05-0.1 mmol/L, 2-5 μg/mL, 5-500 mg/kg, IC_{50} < 1%
Naphthodian-thrones	Hypercin	MAO inh., COMT inh. [64, 77]	σ-opioid, cholinergic, SER, NE [92]	σ receptor, mAChR, NMDA	5-HT, NE	0.01-10 mmol/L, IC_{50} 0.1 mmol/L
Flavonoids Biflavanoids	quercitin, quercitrin, isoquercitin, campherol, hypericide, luteolin, amentoflavone	MAO inh., COMT inh. [64-80]	Benzo, benzo [65, 81, 82]	MAO, Benzo agonist [65, 81, 82]		0.01-10 mmol/L
Phloroglucinols	hyperforin	MAO inh. [84]	5-HT, NE, DA, GABA, GL [84, 93]	5-HT_3* [84]	5-HT, NE, DA, GABA [69, 84]	0.01 mmol/L, 1 μg/mL, IC_{50} = 80-200 nmol/L

MAO = monoamine oxidase, COMT = catechol-*O*-methyltransferase, ACh = acetylcholine, mAChR = muscarinic acetylcholine receptor, NMDA = N-methyl-D-aspartate, 5-HT = 5-hydroxytryptamine, NE = norepinephrine, Benzo = benzodiazepine, GABA = gamma-aminobutyric acid, 5-HT = serotonin, DA = dopamine, GL = glycine, IP3 = inositol triphosphate, IC_{50} = 50% inhibitory concentration, inh. = inhibition, n/a = not available, ns = not specific

*Unproven; hyperforin antagonizes SER-induced (5-HT_3 receptor-mediate) increase in heart rate in rats.

HYPERICUM IN CANCER, HIV, AND BACTERIA

St. John's Wort has other intriguing biologic effects apart from antidepressant action. In vitro studies of HIV-infected cells indicated that hypericin, in the presence of light, inactivates the capsid protein and may have inhibited reverse transcriptase activity. These investigations have progressed to in vivo mouse models [85]. A recent report suggests that hyperforin may possess antibacterial properties [86]. In another study, hypericin was found to have an oncolytic effect when used as a photosensitizing agent in laser phototherapy of mice transplanted with human squamous cell carcinoma [87]. In tissue cultures of malignant glioma cells, hypericin inhibited growth, both in the presence and absence of light [88]. The authors of this study postulated this action resulted from inhibition of protein kinase C, and felt that the results justified clinical trials of patients with malignant gliomas.

SUMMARY

St. John's Wort contains several active, hitherto uninvestigated components, making it a fascinating natural product. There is information to suggest that this plant has some effect in reducing symptoms of mild to moderate depression and anxiety, but how much is not clear. Although the herb appears to have a low degree of risk, it is still unclear whether its benefits will outweigh the risks in the long term. Further controlled trials of effectiveness, side effects, and drug interactions are needed. A full scale three-year, multicenter NIH drug trial now underway may provide some answers to these questions [89, 90]. Its mode of action awaits further clarification. Studies of Hypericum's effects in cancer and viral infections are fascinating but even more preliminary. At the present time preparations are not standardized or regulated in the United States, which makes dosing a problem in this country. The tendency of the public to mix and match various prescriptions drugs and over-the-counter products will undoubtedly lead to some novel, interesting, and dangerous drug interactions.

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