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St. John's Wort: A Success Story

This review discusses the history and current research on St. John's Wort (an herb widely used for treatment of depression), including preclinical investigations, clinical trials and interactions with other medications.

A recent report (1) indicated that interest in herbal products for medicinal purposes has grown dramatically in the Western world. For traditional herbal remedies for Central Nervous System (CNS) disorders, studies have shown that the most popular are those that have been most extensively studied (both clinically and preclinically) and that have been approved for therapeutic use by the health authorities of many Western and other non-US countries. However, although the clinical efficacy of such herbal remedies has been proven, there have been few reports of efforts to develop structurally and functionally novel psycho-therapeutics based on knowledge acquired from herbal remedies. In a systematic analysis published in 1997, it was reported that only 157 of 520 drugs (30%) approved by the US Food and Drug Administration (FDA) between 1983 and 1994 were natural products or their derivatives (2). In addition, this report indicated that when there were focused efforts to discover natural products for clinical use, the level of success rose dramatically. Conversely, there was no success in the absence of targeted programs for natural products. Consequently, no analgesics, antidepressants, anxiolytics or other CNS drugs based on natural products were approved during this 11-year period.

Our current analysis indicates that the situation has not changed much since publication of this report. Although identifying hits and leads from secondary plant metabolites continues to be a major goal of many drug discovery programs, few concentrate on development of CNS therapies. In addition, only a small number of the studies of neurological activities of herbal extracts and their active constituents have been subsequently evaluated in terms of their potential for identifying structurally or functionally novel CNS drugs, the main aim of these studies being evaluation of known CNS herbal remedies in terms of our current understanding of brain functions or identification of their active constituents; that is, generating more evidence to justify their traditional therapeutic applications. However, in light of their proven clinical efficacy and their largely unexplained mode of action, these herbal remedies should receive more attention as readily available sources for structurally and functionally novel sources of CNS drugs. This article summarizes our current knowledge of the major bioactivities and clinical efficacy of St. John's Wort (Hypericum perforatum [HP]) in the hope of stimulating interest in evaluating this herb as a potential source of novel CNS drugs. (For further information, there are a number of books (3, 4) and reviews (5-12) that have nicely summarized our current knowledge on the neurological effects of HP.)

History of St. John's Wort

Hypericum species were known to ancient communities as useful medicinal plants. HP in particular was used throughout the Middle Ages. It flowers at the time of the summer solstice, and in medieval Europe it was considered to have powerful magical properties that enabled it to repel evil. Medicinally, it was used to treat emotional and nervous complaints (13). In European folk medicine Hypericum was also used as an antiphlogistic to treat bronchial and urogenital tract inflammations, hemorrhoids, traumas, burns, scalds and ulcers (12). However, in the 19th century the herb fell into disuse.

The very first report on the efficacy of an HP extract for treatment of depression dates to 1935 (14), much earlier than the fortuitous discovery of similar efficacy for the synthetic tri-cyclic antidepressant imipramine or the MAO inhibitor iproniazide. However, major interest in the use of HP for treatment of CNS disorders did not start until the 1980s when German physicians showed that HP extracts could be as effective as imipramine for treatment of mild to moderate depression, and that HP extracts are better tolerated by patients than many synthetic antidepressants. Following this discovery, extensive efforts (including animal models and clinical trials) were initiated in many German industrial and academic laboratories, the results of which are discussed in this review. As a result of these studies HP has become increasingly popular in Germany. In 1994, 66 million daily doses of HP standardized extracts were prescribed there treatment of depression (15).

Preclinical Studies of St. John's Wort

It is important to emphasize that HP extracts contain multiple constituents and hence, research on HP extracts has focused both on properties of the complete extract as well as on identification and properties of the constituents.

The main therapeutic focus of HP research has been its antidepressant properties. (HP has also shown antidepressant, anxiolytic, anti-amnestic, anti-inflammatory, analgesic, and anti-stress activities in various animal models [8, 16-25]. It has also recently been found that HP has neuroprotective effects, diminishes cognitive impairment and improves spatial learning and memory [19, 22-23, 26-29].) A commercial standardized extract of HP (Psychotonin®) was tested in several animal models predictive of psychotropic activity

(30). Butterweck et al. (31,32) compared the HP extract LI 160 with bupropion, a weak synthetic antidepressant. Similar results were obtained for both drugs in the tail suspension test and in the forced swim test (two standard tests for antidepressant activity). Since HP treatment was antagonized by drugs known to reduce dopamine functional activity (haloperidol, sulpiride, α-methyltyrosine and γ-butyrolactone) the authors concluded that HP extract exerted its activity via dopaminergic activation. Sub-chronic treatment with LI 160 (250 mg/kg for two weeks) resulted in a 15% down regulation of β-adrenergic receptors in the rat frontal cortex. In the same study, a 25% down regulation was observed after the imipramine treatment (33).

Preclinical investigations have reported that HP extract and its components can also inhibit monoamine oxidase (MAO) (34-37). Bladt and Wagner (35) reported that the HP fractions containing the highest concentration of flavonoids showed the greatest MAO inhibition, and further study showed that the flavonoids extracted from HP showed antidepressant activity (38). In another study the xanthone fraction was a particularly strong inhibitor of MAO-A *in vitro* (39). However, the MAO inhibition shown by HP extract may not be pharmacologically relevant since it has not been confirmed *in vivo*; no MAO inhibition was seen *in vivo* after administration of 300 mg/kg HP extract to rats (35). Other proposed mechanisms have involved effects on serotonin. Muller and Rossol (40) reported that HP extract inhibits serotonin (5-HT) receptor expression in a neuroblastoma cell line at 50 μM (~25 μg/ml), and Perovic and Muller (41) reported inhibition of 5-HT uptake (IC_{50} = 6.2 μg/ml). However, a concentration of 25 μg/ml could never be achieved in a whole animal, and even 6.2 μg/ml seems unlikely. (For comparison, Muller et al. [33] reported an IC_{50} for the synthetic antidepressant, clominpramine, of 0.9 nM [0.3 ng/ml] for 5-HT uptake inhibition.) In addition, inhibition of both synaptosomal GABA uptake (IC_{50} = 1μg/ml) and $GABA_A$ receptor binding (IC_{50} = 3 μg/ml) was noted. In receptor radio-ligand binding studies, crude HP extract showed significant receptor affinity for adenosine, $GABA_A$, $GABA_B$, serotonin, benzodiazepine, inositol triphosphate (IP_3), and MAO-A, B (42). Conversely, synthetic hypericin (95%) (a component of HP extract previously associated with the antidrepressant activity of HP extract) lacked significant MAO-A or MAO-B inhibition at concentrations up to 10 mM. Hypericin had affinity only for N-methyl-D-aspartate (NMDA) receptors (Ki-1μM), and this may play a role in its reported antiviral activity since NMDA antagonists prevent gp-120 induced neurotoxicity (43).

More recently, many studies have supported the idea that antidepressant activity of the HP is due to hyperforin (a prenylated phloroglucinol) rather than hypericin (44-60). Hyperforin was shown to inhibit uptake of 5-HT, dopamine (DA), norepinephrine (NE), GABA and L-glutamate with IC50 values of about 0.05 - 0.10 μg/ml (5-HT, NE, DA, GABA) and about 0.5 μg/ml (L-glutamate) in synaptosomal preparation (45, 60). Other studies showed that hyperforin releases acetylcholine (61, 62). (HP reduces the degradation rate of acetylcholine [63].) A recent study from our lab indicated that hyperforin may be a potential neuroprotective agent that blocks activation of NMDA-type glutamate receptors (64, 65). Further studies testing the possible effect of hyperforin in protein kinase C-mediated responses and in vivo experiment(s) to evaluate hyperforin as a potential inhibitor of water transport are in progress (unpublished).

Although the vast majority of recent reports on potential psychotherapeutic uses of this herb and its CNS-active constituents concentrate around hyperforin only, it cannot be overemphasized that several other therapeutically interesting CNS-active HP constituents have already been identified, and that none of the therapeutically interesting pharmacological properties of HP extracts can yet be properly explained by what is currently known about their bio-active constituents. In addition, available quantitative data on antidepressant effects of hyperforin and HP extracts strongly suggest that, quantitatively, the contribution of hyperforin to the observed antidepressant efficacy of HP extracts must not be a major one. (Indeed, it has been shown that hyperforin-free HP extract has antidepressant effects [55].) It must also be remembered that, as noted above, hyperforin and HP extracts have been shown to treat CNS disorders other than depression (29). Therefore, drug discovery projects based on HP should not be limited to hyperforin and should not be limited to antidepressants.

Clinical Trials

Pharmacokinetic data of an HP extract containing hypericin, pseudohypericin, hyperforin, the flavonoid aglycone quercetin, and its methylated form isorhamnetin were obtained for all five listed constituents in healthy human volunteers following either a single oral dose or a multiple once-daily dose over a period of 14 days (66). After a single dose of 900 mg dry extract, a maximum plasma concentration (C_{max}) of 3.8 ng/ml was reached for hypericin in approximately 8 hrs, and the elimination half-life found to be 18.7 hrs. For hyperforin, a C_{max} of 122 ng/ml was reached in 4.5 h with an elimination half-life of 17.5 hr. Similar results were obtained for the multiple dosing. In a separate study, the pharmacokinetics of hyperforin were studied in human volunteers after oral administration of 300 mg/kg HP extract (47). A C_{max} 150 ng/ml was reached 3.5, with elimination half-life of approximately 9 hours. The pharmacokinetics was linear up to 600 mg of the extract, with non-linearity observed for higher doses. Plasma concentration curves in human volunteers fit well into an open two-compartment model.

In another pharmacokinetic study on human volunteers, hypericin or pseudohypericin was not observed in urine or after incubation of urine with glucuronidase and sulfatase (67). From the chemical structure and molecular size, the authors concluded that these compounds were probably conjugated with glucuronic acid eliminated through bile.

HP has been tested in multiple clinical trials against placebos and synthetic antidepressants (9-11, 68-70, 73-76, 80-83). German researchers have published a meta-analysis of 23 randomized trials of HP with a total of 1, 757 outpatients with mild to moderate depression. They concluded this herb was significantly superior to placebo and appeared comparably effective to standard synthetic antidepressants (maprotiline, imipramine and amitriptyline) while producing fewer side effects (11). In a double blind study conducted at seven German medical clinics, physicians treated 240 patients with mild to moderate depression for six weeks – one group of 114 patients with HP, and the other 126 patients with Prozac. While the two medications showed similar efficacy, there were significant differences in side effects. 23 percent of the study population taking Prozac reported side effects, including gastrointestinal problems, vomiting, dizziness and erectile

dysfunction, while only 8 percent of patients in HP therapy reported side effects (mostly GI distress) (81).

HP has an excellent safety profile that is clearly superior to many conventional antidepressants (84). However, in recent years, multiple case reports and clinical studies in herb-drug interactions have been published (5, 85-89). Several preclinical reports have demonstrated that many bio-active constituents of HP extracts can modulate activities of hepatic drug metabolizing enzymes (particularly CYP3A4), and the P-glycoprotein drug transporter (90-92). These results are consistent with reports that clinically relevant drug interactions may occur when St. John's Wort is co-administered with other drugs, in particular with agents predominantly metabolized by CYP3A4 and P-glycoprotein at the same time (5, 88). These interactions with HP can decrease the plasma concentrations of a number of important prescription drugs, including the HIV protease inhibitor indinavir, the reverse transcriptase inhibitor nevirapine (another HIV drug), Xanax (anxiety), fexfenadine (allergies), Zocor (cholesterol), cyclosporine and tacrolimus (immunosuppresants), warfarin and phenprocoumon (blood thinners), digoxin (congestive heart failure), and oral contraceptives, with possible clinically serious consequences. Some evidence indicates that the combination of HP and selective serotonin re-uptake inhibitors may lead to serotonin overload or to the serotonin syndrome, particularly in elderly patients (5, 85, 88). However, although these reports strongly suggest that co-administration of some drugs with HP extracts requires caution, it should be noted that many other psychoactive drugs also show drug-drug interactions in addition to other more serious side effects. Since all properly-controlled clinical trials in patients with mild to moderately severe depression have consistently demonstrated the efficacy and a very high safety margin of diverse types of HP extracts with drug-drug interaction as the only potential side effect, these extracts can be considered one of the safest known psychotherapeutic agents with proven clinical efficacy, according to the modern concept of "evidence-based medicine." Whether it is more effective than the 20-plus available synthetic antidepressants requires further study, but it is an option for patients who may not be willing to try those alternatives. With fewer than 50% of depressed patients treated adequately, as is the case for most Western societies, it is believed there is much scope for such a "natural" treatment, if it is effective and its risk/benefit ratio is acceptable.

And The Story Goes On…

It is now becoming exceedingly apparent that currently available psychotherapeutics do not properly meet the therapeutic demands of the vast majority of patients with mental health problems, and that herbal remedies may be a viable alternative for many such patients, both in the Western world and elsewhere. Detailed analysis of our current understanding of the most popular and best studied CNS-active medicinal plants shows that many critical pharmacological questions remain to be answered. However, clinical efficacy has been demonstrated for many of them, including St. John's Wort. Consequently, many phyto-pharmaceutical laboratories are now focusing their efforts on identifying the active constituents and modes of actions of these herbs. The aim of most of these efforts has been to obtain a patentable, or more therapeutically useful, or better standardized extract. However, until now very little effort has been made to develop structurally and/or functionally novel CNS-active drugs. The information summarized in this review strongly suggests that this situation could be hindering the progress of CNS drug discovery projects. Future research regarding St. John's Wort and other herbs has to fill the gaps left by existing clinical trials, such as effectiveness for more severe depression, long-term effectiveness, and safety. In addition, pharmaceutical and pharmacological research on product comparability and mechanisms of action is needed to harmonize the clinical data. Given the enormous public interest and the pharmaceutical industry's financial interest, it now seems possible that adequate resources will be available for such research.

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