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Hypericum perforatum Extracts as Potential Antidepressants

BENEDETTO VITIELLO

National Institute of Mental Health, Room 7147, 6001 Executive Boulevard, Bethesda MD, USA

Abstract

Extracts of *Hypericum perforatum* have been used in the treatment of mild to moderate depression for many years in Europe. More recently, these extracts have become available in the USA as dietary supplements and have been popularly used to improve mood. In support of this practice, data from several controlled clinical studies suggest that *Hypericum perforatum* is better than placebo and as effective as established antidepressant drugs. These data have, however, several limitations that should temper our enthusiasm and argue for more research before accepting *Hypericum perforatum* extracts into our pharmacopoeia of established antidepressants. Extant data on the possible effects of *Hypericum perforatum* extracts in depression are here critically reviewed and plans for further research presented.

Hypericum perforatum is a plant that is commonly found in the wild throughout Eurasia and North America. It has been known for centuries for its putative medicinal properties, including, among others, wound-healing, diuretic, antibiotic, antiviral, and antidepressant effects. Because the flowers bloom around St John's Day (June 24), it is popularly called St John's Wort. The aerial portion of the plant is harvested just before or soon after its blossom, inclusive of flowers and buds. It is then dried following one of several different methods (American Herbal Pharmacopoeia and Therapeutic Compendium 1997). Conditions of plant growing, time of harvesting and temperature, humidity, and light exposure during the drying process all have a significant impact on the chemical composition of the final product. Infusions, tinctures, oil preparations, and standardized extracts can be prepared from the dried plant. For depression, standardized extracts have been most commonly used. There are various methods of extraction. The most common involve ethanol or methanol extraction. The latter can extract about 75% of hypericin from the plant (Wagner & Bladt 1994). After extraction, the alcohol is evaporated and the extract is formulated into tablets, capsules, and syrups for oral administration.

E-mail: bvitiell@nih.gov

There is no consensus on the mechanism of action of the *H. perforatum* extracts or on the active ingredient that can account for the possible antidepressant effect. In-vitro binding to many neurotransmitter receptors has been reported, but, with the exception of $GABA_B$ receptors, significant binding occurs only at micromolar concentrations that are unlikely to be reached in clinical use (Cott 1997; Muller et al 1997). This is the case also for monoamine oxidase inhibition, which therefore does not seem to be clinically significant. There are at least seven groups of compounds for which some bioactive effects have been reported (Nahrstedt & Butterweck 1997). These compounds can be quantitatively measured by high performance liquid chromatography, thus allowing standardization across batches. Traditionally, attention has been paid to two naphthodianthrones: hypericin and pseudohypericin. There is evidence that they account for hypericum-induced photosensitization (Brockmoller et al 1997) and reduce the immobility time of rats in the forced-swimming test, an accepted model for screening antidepressant drugs (Butterweck et al 1998). Most commonly, commercial extracts of *H. perforatum* are standardized on a total content of hypericin (that is, the sum of hypericin and pseudohypericin) around 0·1–0·3%. Naphthodianthrones are not, however, the only biologically active compounds in *H. perforatum*, nor the most abundant. Flavonoids, such as rutin,

quercetin and quercitrin, account for 2–4% and phloroglucinols, such as hyperforin and pseudohyperforin, for 1–6% of the extract (American Herbal Pharmacopoeia and Therapeutic Compendium, 1997). Hyperforin has been recently proposed to be most relevant to the antidepressant activity of *H. perforatum*, based on reports of its activity in the forced-swimming test as a monoamine uptake inhibitor (Chatterjee et al 1998; Muller et al 1998). Because it is highly unstable when exposed to light and air, the content of hyperforin in the commercial preparations of *H. perforatum* varies considerably.

The bioavailability and pharmacokinetics of hypericin and hyperforin following oral administration of *H. perforatum* extracts in humans have been described. Elimination half-life is about 24 h for hypericin (Staffeldt et al 1994) and 9 h for hyperforin (Biber et al 1998).

Efficacy data

At least 26 randomized clinical trials of *H. perforatum* extracts in depression have been reported. Of these, 23 were double-blind, one single-blind, and two open. Sixteen studies were placebo-controlled, while the others had a standard psychoactive agent as a control. These studies were usually conducted in general practice or in psychiatrist offices, and included outpatients without severe depressive symptoms, such as suicidal ideas, psychosis, or severe dysfunction. A meta-analysis was conducted on 23 studies (Linde et al 1996). However, three studies tested combinations of *H. perforatum* extracts and other natural products, such as valerian, and three others did not report information on the number of treatment responders. Moreover, two of the latter three studies were not blinded and used a benzodiazepine agent as control. Another study was single-blind. Of the remaining 16 studies, 13 were placebo-controlled and three used a standard antidepressant as control. Doses of Hypericum extracts ranged from 350 to 900 mg per day and the most common administration schedule was 300 mg three times a day. If the number of responders is considered in these 13 placebo-controlled studies, *H. perforatum* was better than the placebo in ten studies. When all the patients of these 13 studies are pooled (n = 828), 55% were responders in the *H. perforatum* group and 22% in the placebo group. The three antidepressant-controlled studies found similar response rates in the *H. perforatum* group (range 53–80%) and in the standard antidepressant group (range 54–70%). When all the patients of these three studies are pooled (n = 317), the response rate was 64% for *H. perforatum* and 58% for the standard antidepressant.

These figures can appear impressive and may be interpreted as evidence of clear efficacy of *H. perforatum* extracts as antidepressants. Several considerations are, however, necessary. First, the diagnostic criteria used in most of these studies do not permit extrapolation of the results to general clinical patients suffering from depression, at least based on the standards in use in the USA. Only two of the above discussed 16 studies enrolled patients who met diagnostic criteria for ''major depression'' based on the Diagnostic and Statistical Manual, edition III, or revisions III-R and IV (American Psychiatric Association, 1980, 1987, 1994). The other 14 studies included patients with ''neurotic depression'', ''adjustment disorder'', or ''reactive depression'', according to ICD classification, or used no diagnostic criteria at all (in three studies). Thus, even if changes on accepted rating scales of depressive symptoms, such as the Hamilton depression rating scale, were detected during the administration of *H. perforatum* extracts, it remains unclear if these extracts have clinically significant antidepressant effects in patients suffering not only from depressive symptomatology, but also from a depressive disorder. Second, the duration of these studies has been, in most cases, limited to four weeks. Only four studies lasted six weeks and one eight weeks (Linde et al 1996). Thus, there is no experimental documentation of sustained therapeutic activity beyond an acute treatment phase. Third, these studies often had a small sample size. In fact, only four of the 16 studies enrolled at least 50 patients in each treatment arm. In some cases, it is surprising to find reports on 0% response rate on placebo (Halama 1991 and Osterheider 1992 as reviewed in Linde et al 1996). In fact, placebo response in clinical trials of antidepressants is known to range from 30 to 60%. In several placebo-controlled studies, liquid preparations of *H. perforatum* were utilized. Because, *H. perforatum* extracts often have a peculiar taste, some unblinding of the patient can be suspected. Fourth, given that the placebo response rate can be quite high among depressed patients, finding a comparable response rate for Hypericum and for a standard antidepressant in a non placebo-controlled trial cannot be interpreted as evidence of Hyperi-cum efficacy. The possibility remains that both treatments were ineffective, that is not different from a placebo, had this been included in the experiment. This doubt becomes even more legitimate, if one considers that the doses of standard antidepressants used as comparators in these studies (imipramine 50 or 75 mg per day and maprotiline 75 mg per day) were below the usual therapeutic dose range of these drugs. Finally, one should also mention that

different preparations of *H. perforatum* were tested in these trials. Seven different products were used in the 16 studies thus far discussed. The authors of the 1996 meta-analysis concluded that there was still inadequate evidence of the efficacy of *H. perforatum* extracts as antidepressants.

Since the publication of the influential meta-analysis of Linde et al (1996), three additional randomized double-blind studies have been reported, of which two included a standard antidepressant and one a placebo as control treatment arms. A study compared the efficacy of a commonly used *H. perforatum* extract (LI 160) with amitriptyline in 156 patients with DSM-IV major depression (American Psychiatric Association 1994; Wheatley 1997). The *H. perforatum* extract was given at the fixed dose of 300 mg three times a day and the amitriptyline dose was 25 mg three times a day. The double-blind trial lasted 6 weeks. A patients with at least a 50% decline from the Hamilton depression rating scale (HAMD) score at entry, or a final score below 10, was judged a responder. The response rate was 60% in the Hypericum group and 78% in the amitriptyline group ($P = 0{\cdot}64$). At the end of the study, the HAMD score was lower ($P < 0{\cdot}05$) in the amitriptyline group. Thus, in this large, well conducted study, despite the relatively low dose of amitriptyline, this antidepressant showed some signs of superiority over the *H. perforatum* extract. As already pointed out, no clear inference as to the efficacy of the extract can be drawn in the absence of a placebo group.

In another recently published study (Vorbach et al 1997), 209 patients with major depression (ICD-10 criteria) were randomized to a 6-week trial of LI 160 (1800 mg per day) or imipramine (75 mg per day). This study is remarkable for the inclusion of patients with more severe symptomatology, as evidenced by a mean HAMD entry score of about 25, and for the use of a higher dose of *H. perforatum*. The HAMD scores declined in both groups without a statistically significant difference. The improvement score of the clinical global impression (CGI), as a scale commonly used to define response, showed a trend in favour of imipramine ($P = 0{\cdot}079$). The response rate, using the CGI, was 61% in the *H. perforatum* group and 71% in the imipramine group. It should be pointed out that a daily dose of imipramine of 75 mg is probably considered by most practitioners as rather low especially in patients with more severe depression.

Finally, an interesting placebo-controlled study has tested the efficacy of two preparations of *H. perforatum* that differed in hyperforin content (Laakman et al 1998). Patients with DSM-IV-defined major depression were randomly assigned to receive an extract with 0·5% hyperforin, another extract with 5% hyperforin, or placebo for 6 weeks. The decline of the HAMD score was significantly greater in the group assigned to the high hypericin extract than in the placebo group. The decline in the low hypericin group was not significantly different from the decline in the placebo group. Based on the CGI improvement score, the response rate was 70% in the high hyperforin group, 55% in the low hyperforin group, and 48% in the placebo group. These data suggest that hyperforin content may be a critical component of *H. perforatum* for antidepressant activity. If this finding is replicated, standardizing *H. perforatum* extracts for hypericin content will become essential.

Safety

All the clinical studies of *H. perforatum* extracts have found these products to be remarkably safe and devoid of serious adverse events (Woelk et al 1994). Non-specific gastrointestinal symptoms and allergies have been reported, but in placebo-controlled studies, *H. perforatum* extracts were not associated with more adverse events than placebo (Linde et al 1996; Laakman et al 1998). When compared with tricyclic antidepressants, *H. perforatum* extracts are clearly better tolerated and cause no cardiac conduction abnormalities (Czekalla et al 1997; Vorbach et al 1997). A specific adverse event is the increase in skin photosensitivity that hypericin causes in a dose-dependent manner (Brockmoller et al 1997). This effect can be a clinically significant problem for patients with fair skin treated with high doses of *H. perforatum* extracts (i.e. 1800 mg per day and above) and exposed to intense sunlight. The general safety and tolerability of *H. perforatum* extracts found in clinical studies is paralleled and confirmed by the results of the toxicity studies conducted in animals by private companies that market these extracts (unpublished reports). The safety of concurrent administration of *H. perforatum* with prescription or over-the-counter medications has not been studied and, even if there are no theoretical reasons to expect specific interactions, adverse reactions cannot be excluded when products are used in combination.

Further research initiatives

In the USA, considerable interest has arisen in *H. perforatum* extracts as potential antidepressants. Many extracts are commercially available to the public as dietary supplements. At the moment, products marketed as ''dietary supplements'' are

not regulated by the Food and Drug Administration in the same way as drugs are. In particular, there is no requirement to prove their efficacy and safety in patients. As a consequence, no commercial claims can be made that the extracts are indicated in the treatment of medical conditions. As a matter of fact, because they are available on the market as dietary supplements and are relatively inexpensive, people have used them as mood enhancers. The possible use of these products by patients suffering from major depression raises the most concern. Major depression is a serious and common disorder that affects more than 17 million people in the United States. It can lead to severe suffering, social dysfunction, and, in extreme cases, suicide. There are both pharmacological and psychotherapeutic treatments of proven value in the treatment of depression. It is therefore of concern if patients shun standard treatments for a possibly less effective dietary supplement. It is for this public health need, in addition to the undoubtedly intriguing data that already exists on *H. perforatum*, that the National Institute of Mental Health and the National Center for Complementary and Alternative Medicine at the National Institutes of Health are sponsoring a large placebo-controlled trial of a well characterized *H. perforatum* extract. Because selective 5-hydroxytryptamine reuptake inhibitors have become the most commonly used antidepressant drugs in the United States, the study will also include a group of patients on sertraline as the active control arm. Thus, a total of 336 patients suffering from DSM-IV major depression will be randomly assigned to receive an *H. perforatum* extract, sertraline, or placebo for eight weeks. At the end of this acute phase, the patients who have responded to the assigned treatment will continue blindly on it for another four months. The starting dose of *H. perforatum* is 900 mg per day and can be gradually increased based on the individual patient response up to a maximum of 1800 mg per day. Similarly, the sertraline dose can vary from an initial 50 mg per day to a maximum 150 mg per day. The trial is statistically powered to compare the efficacy of *H. perforatum* vs placebo. The sertraline arm serves as the active control in the experiment. Both acute and long-term effects of *H. perforatum* will be studied. The study is coordinated by the Duke University Medical Center (Principal Investigator Jonathan Davidson) and conducted at 12 clinical sites across the United States. Results are expected in about 2 years.

Other controlled studies are either in progress or in preparation under private industry sponsorship in the USA. They attest to the great interest that *H. perforatum* extracts have generated.

Conclusions

The extant data on the efficacy and safety of *H. perforatum* extracts in treating depressive symptoms are of remarkable interest, but, for the discussed limitations of the clinical studies, are still not convincing of the value of these extracts in treating clinically depressed patients. One large study has been launched in the USA under the sponsorship of the National Institutes of Health (National Center for Complementary and Alternative Medicine) with the goal of providing a definitive answer as to the efficacy of a well-characterized *H. perforatum* extract in major depression. Still unresolved is which are the pharmacologically active components in this herb responsible for its effects on mood. According to how this question is answered, the current standardization of *H. perforatum* extracts based on hypericin content may not be the most relevant to the putative antidepressant activity.

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