HYPERICUM AND THE BRAIN

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ABSTRACT

Various species of Hypericum, particularly *H. perforatum*, exert useful clinical activity in a number of brain-related disorders. Patients with mild to moderate depression have been the most extensively investigated in this regard. Other trials have looked at treating persons affected by seasonal affective disorder as well as early investigations in brain neoplasms. A number of studies have attempted to define which constituents act in what ways to achieve observed clinical outcomes, with no definitive answers yet being available in most cases. This paper reviews the work already done in these areas, including the safety profile and clinical application of Hypericum.

REVIEW

Popular press attention in the United States finally caught up with *Hypericum perforatum* (St. John's wort) in 1997. While St. John's wort products outsold fluoxetine (Prozac®) by four times in Germany in late 1997 (1), this valuable herb remained relatively obscure elsewhere in the world. This had changed by December 1997, at least in the USA, because of mass media articles and the recent publication of the American Herbal Pharmacopoeia's first official monograph, which was on Hypericum (2).

Most health care practitioners in the complementary medicine field have at least passing familiarity with the use of *Hypericum perforatum* to treat patients with depression. This effect has been demonstrated repeatedly in clinical trials, as will be reviewed below. This medicinal plant clearly must have an impact on the nervous system to be so consistently effective in treating depression. Ongoing investigations are trying to determine exactly how Hypericum accomplishes what it does. These proposed mechanisms of action of Hypericum and its constituents on the central nervous system related to mood disorders and neoplasms remain to be fully developed. This paper attempts to clarify what is currently understood.

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Two important and more general issues must be addressed first, as Hypericum illustrates dilemmas in the modern application of phytomedicines. First, though much research has focused on one species, *H. perforatum*, mounting evidence suggests that other species may be just as effective and valuable (3). Among these alternate, potentially effective species are *H. calycinum* (rose of Sharon), *H. hirsutum*, *H. olympicum* and *H. patulum* (3,4). Over 400 species of Hypericum exist worldwide. As yet the market place has not achieved the level of quality in which the actual source species for most herbal medicines are identified in any rigorous fashion. In the future this will become more and more important, particularly if one species is shown to be preferable to another but they are difficult to differentiate. Hypericum is only the tip of this iceberg. The term Hypericum will be used throughout to highlight the fact that no single species can yet be definitively identified as the best medicine, though most research has been on *H. perforatum*.

Hypericum also clearly shows why it is a problem to fixate on single "active constituents" from medicinal plants. In a few cases it may be that one compound out of the thousands found in a plant species may provide the vast majority of the direct therapeutic activity. However, even if other constituents in a plant do not have direct actions, they may have important indirect effects such as

improving absorption, reducing toxicity or altering metabolism of directly active chemicals. This remains highly theoretical as almost no scientific investigation of this hypothesis has been carried out. What study of Hypericum clearly highlights is that there is almost certainly more than one group of active constituents in the plant than just hypericin and related dianthrones (4). As has been stated elsewhere, "Work in recent years, including some human trials, has shown that the whole-plant extract of St. John's wort is more effective than extracts that just focus on the hypericin" (5). Fortunately Hypericum extracts standardized for hypericin did not lead to severe reduction of the flavonoids, another major group of active compounds in the plant, at least as far as the antidepressive action goes. The same might not be true in the future with other medicinal plants or extracts.

Hypericum and the Brain in History

When Hypericum came into use as a mood-altering agent remains unclear. Ancient medical texts in Greek do not cite this plant for use in any specific mental conditions (6). However, it was often cited as being beneficial in driving away "demons" (7), which was sometimes a way of describing various forms of mental diseases before psychologic or psychiatric science existed. *Hypericum perforatum* is not native to the Americas, but other indigenous species of Hypericum were employed by the Native Americans for their non-psychoactive properties. These consisted primarily of using the oil for wound healing, similar to reports in the herbal literature of Europe (7).

The first references to using Hypericum for depression began to appear in North America in the late 1800s. The Eclectic physicians of the United States employed quite a number of botanical remedies, though they used Hypericum only occasionally. For example, King mentions the use of Hypericum for depression (8). It is simply unknown how this use was discovered. Whatever the means, it has now been firmly established in human clinical trials and whoever made the initial observation deserves hearty thanks for setting medicine on the trail of this useful treatment.

Clinical Trials of St. John's Wort for Depression

Two extensive reviews of the clinical trials performed using a variety of standardized extracts of Hypericum have been published. The first of these concluded from an analysis of eleven studies, eight placebo-controlled and three comparing the extracts to drug antidepressants, that Hypericum is an effective treatment for mild to moderate depression with fewer adverse effects than drugs (9). A more advanced meta-analysis found that in 15 placebo-controlled and eight antidepressant drug-controlled trials, Hypericum extracts were more effective than placebo and as effective as standard drugs (10). The total number of patients studied was 1,757. While 19.8% of patients taking Hypericum extracts reported side effects, 35.9% of those taking drugs did also. A total of 0.8% of patients randomized to take Hypericum dropped out due to adverse effects compared to 3% of those randomized to antidepressant drugs.

Extracts of Hypericum standardized to provide 0.5-2.7 mg of hypericin daily were utilized in the clinical trials for depression. One such extract was also shown to have benefit in combination with phototherapy for patients with seasonal affective disorder (11). As there was no placebo control in this trial, the results are not definitive. This trial has not been confirmed by other groups to the author's knowledge. An interesting side note here regards the concern about inducing photosensitivity with hypericin-rich extracts. No patient in the study, some having been exposed to as much as 3,000 lux for two hours daily in combination with the extract, developed any sign of photosensitivity over four weeks time.

The Photosensitivity Question

The initial trials of intravenous hypericin in patients infected with human immunodeficiency virus (HIV) suggested that a sufficient dose for antiviral effects could not be achieved without inducing severe reactions to daylight (12). A dosing trial involving four white HIV+ patients found that injection of 0.5 mg/kg of hypericin led to development of acute facial pain and erythema in two of the volunteers after 2-3 doses (13). The problem occurred once sunlight was encountered directly or through glass. One patient receiving 0.25 mg/kg for 13 weeks eventually developed hand pain and erythema when exposed to sunlight. The fourth patient had his minimal erythema dose determined before and after hypericin, and hypericin definitely lowered it.

Surprisingly, other, larger trials of intravenous (IV) hypericin combined with orally administered Hypericum standardized extracts did not encounter any such adverse effects (14, 15). The IV doses used were similar to those in the dosing trial mentioned above (13). There were significant improvements in CD4+ cell counts in 16 of 18 patients in one study involving twice weekly injections of 2 ml of hypericin (supplying 0.4-0.6 mg of hypericin) and three caps of Hypericum extract twice daily (14). No opportunistic infections were noted over the 40 months of the study. Another trial showed that intravenous hypericin combined with oral dosing could lead to reductions in HIV viral load in many patients over three years (15).

One trial looking at orally administered hypericin did not encounter photosensitivity reactions. An observational study of 31 HIV+ patients taking 1 mg hypericin per day found all those who had never taken zidovudine had consistently maintained elevations in CD4+ cell counts over five months (16). Five subjects experienced reversible elevations of serum liver enzyme levels in this study, an adverse effect not noted elsewhere. Another study of oral intake of a high-hypericin extract in healthy volunteers found no increase in photosensitivity at usual anti-depressant doses (<5 mg hypericin daily) (17).

From these data it seems apparent that the vast majority of persons taking even high doses of hypericin will not develop phototoxic reactions. Nevertheless, light-skinned persons are advised to use caution when taking hypericin-containing products, particularly for the first time, and to avoid strong sun and ultraviolet light (e.g., tanning booth) exposure.

Hypericum: How Does It Inhibit Depression?

The question of how Hypericum and its many active compounds can alter brain chemistry to bring about its clinical effects continues to be debated (see Table 1). There were

initially reports that Hypericum extracts might be significant monoamine oxidase (MAO) inhibitors (18). Though these authors believed the result was due to hypericin, the extract they employed was only 80% hypericin. Further investigations have confirmed that hypericin does not inhibit MAO, though the flavonoids and possibly other compounds in Hypericum may have *in vitro* anti-MAO activity (19,20). Unfortunately, the xanthones and flavonoids found to inhibit MAO-A are present in such small quantities in Hypericum it is very unlikely they would have a significant effect along these lines *in vivo* (20,21).

Flavonoids and xanthones also appear to inhibit catechol-o-methyltransferase (COMT), an enzyme which performs a similar function in the central nervous system to MAO, but again the concentrations necessary virtually preclude this as a significant effect in humans (21). These findings, combined with the virtual absence of any reports of people taking Hypericum developing the types of adverse effects one expects from MAO inhibiting drugs, have more-or-less put to rest the theory that Hypericum elevates mood by acting on MAO alone.

Another theory of the antidepressant action of Hypericum involves serotonergic neurons, which are well known to be involved in mood. *In vitro* studies have shown that crude extracts of Hypericum inhibit serotonin reuptake (22). Furthermore, Hypericum extracts standardized on hypericin can suppress serotonin receptor expression, particularly when interleukin-1 (Il-1) is added (23). Unfortunately, both of these studies employed concentrations far beyond what can be realistically achieved in humans. Thus it seems unlikely, as far as research has determined, that serotonin-mediated effects alone are significant in Hypericum's mood elevating activity.

This leaves four main hypotheses about how Hypericum can affect depression. First, it may be that Hypericum acts by a number of different routes, with multiple constituents responsible. This possibility was suggested by an *in vitro* study in which an Hypericum extract moderately reduced serotonin and norepinephrine reuptake and weakly inhibited MAO (24). Even very weak MAO and serotonin reuptake inhibitors may have synergistic effects sufficient to explain *in vivo* efficacy. As yet this remains unproven.

Second, Hypericum may act by affecting gamma-aminobutyric acid (GABA) receptors. In vitro evidence suggests that concentrations achievable from tinctures may be sufficient to affect GABA receptors in humans (2). Hypericin-standardized extracts were previously reported to inhibit uptake of GABA in synapses as well as to inhibit GABA-A receptor binding (2). GABA is definitely involved in depressive illness (25), but as yet it is unclear if depressed patients who improve while taking Hypericum do so solely because of GABA-related actions of the plant.

A third hypothesis involves cytokines such as interleukin-6 (Il-6) which, as messenger molecules in the communication network between the brain and the immune system, are involved in the pathophysiology of depression (26). *In vitro*, Hypericum standardized extracts can clearly suppress Il-6 secretion in response to phytohemagglutinin stimulation using blood obtained from healthy and depressed persons (27). Il-1 secretion was also suppressed in the blood of two of four depressed patients, but in none of the blood samples from healthy people (27). Further research, both laboratory and clinical, will be necessary to sort out the mode of action of Hypericum in depression.

The final theory is that Hypericum may act by a mechanism no one has even begun to explore yet. Because the mechanisms behind depression are extremely complex and individually variable, it seems likely that the full reason for the effect of even the most common pharmaceutical antidepressants is not completely known. Only by further clarifying why people become depressed will potentially unknown mechanisms of action be revealed. A hint in this direction was the finding that, in healthy volunteers, after three weeks of supplementation with an Hypericum extract there was a significant elevation in melatonin levels (28). The possible role of melatonin in depression is unknown but intriguing. For the time being, it is not known how Hypericum acts, though there are several possibilities that are being pursued.

Hypericin Against Brain Tumors

Another central nervous system disease, though not primarily psychiatric in its dimensions, is brain cancer. In this section, the potential for treating various types of brain cancer using hypericin-containing extracts will be reviewed.

Hypericin and pseudohypericin derived from *Hypericum erectum* inhibit protein kinase C (PKC) *in vitro* (29). Hypericin has been shown to significantly inhibit the growth of glioma cell cultures, though it was unclear in this study if this was due to PKC inhibition (30). In fact, this study suggested hypericin acted by inducing apoptosis in the glioma cells. Hypericin was as effective as tamoxifen in comparable concentrations in this study. When the glioma cells were exposed to light, hypericin was marginally (13%) more effective than when the cells were kept in the dark.

In contrast, previous studies indicated that light significantly contributed to the tumor destroying (31) and antiviral (32) effects of hypericin. This may be because part of hypericin's action is to produce singlet oxygen radicals when exposed to visible light (33). Animal studies involving squamous cell carcinoma strongly suggested light was necessary for the anticancer action of hypericin (34). Light and oxygen were both necessary for *in vitro* killing of mouse mammary cancer cells (35). Light was also considered very important in the PKC inhibition of hypericin related to its antiretroviral effects in mice (36).

Hypericin also inhibits the growth of neuroblastoma cells *in vitro* by stimulating apoptosis (37). It was not effective in an assay involving human leukemia cells (38), suggesting a specific effect for hypericin in brain but not other cancers. Hypericin also effectively inhibits PKC and induces apoptosis in minute levels (100 nM) in pituitary adenoma cells (39). Even at much higher concentrations in this study, normal fibroblasts were not harmed in any way by hypericin. This provides evidence for the specificity of the cytotoxicity of hypericin in aplastic but not healthy cells.

Hypericin may also exert antineoplastic activity by inhibition of receptor tyrosine kinase (40). It appears to enhance radiosensitivity of glioma cells *in vitro*, without hampering growth of or increasing radiosensitivity of normal fibroblasts (41). All these effects, together with PKC inhibition, may contribute to hypericin's anti-brain cancer action.

So far, clinical data on the efficacy of hypericin or Hypericum in patients with brain cancer are

scanty. One case study reported that a patient with malignant glioma underwent surgical removal of the tumor followed by a course of radiation therapy and then tamoxifen administration (42). Eventually the tumor recurred and was shown to be resistant to tamoxifen. However, it was sensitive to hypericin. It is unclear why a tumor which was resistant to one PKC inhibitor wouldn't be to another, but it suggests hypericin may act by mechanisms different from those of tamoxifen. Due to Food and Drug Administration (FDA) regulations, hypericin was not given to this patient. A clinical trial is currently ongoing in California, but it has run into difficulties, apparently because light is important for the *in vivo*, anti-cancer effect of hypericin (43).

Conclusions

Hypericum spp. constitute a valuable remedy for patients with several central nervous system disorders, particularly mild to moderate depression. Ongoing research will help clarify other indications, including for patients with seasonal affective disorder or brain neoplasms. Hypericum also has potential uses for people with conditions affecting systems other than the brain and spinal cord not addressed here. Several classes of active constituent are present in Hypericum including the highly-touted hypericin and pseudohypericin, but also flavonoids and xanthones at the very least. The actions of these compounds in the human nervous system will require further testing to clarify, but it is likely they have several different actions which combine to give the final clinical result.

Regarding toxicity, there are no nervous system-specific problems other than the potential for interaction with antidepressant drugs with similar actions. There are no published reports of serotonin syndrome occurring when Hypericum crude or standardized extracts are combined with selective serotonin reuptake agents. There are also no available reports of toxicity from combining Hypericum and MAO inhibitors or tricyclic antidepressants. Though such interactions may have occurred but not been reported, they are likely few and far between. Phototoxicity is an extremely rare complication of oral therapy with Hypericum but practitioners should be aware of the potential. As with any medicinal herb, Hypericum can cause gastrointestinal upset and hypersensitivity reactions in susceptible patients. There is presently no information as to whether Hypericum is safe in pregnancy or lactation, so it is probably best avoided unless absolutely necessary. If practitioners are aware of potential adverse effects and interactions they can help patients avoid them, or better understand the origin of them if patients present with complications.

Typical dosing of extracts standardized to 0.3% hypericin is 300 mg three times a day (10). The goal is to provide approximately 1 mg of hypericin daily using such extracts, though this may not be the best approach in light of research reviewed above casting doubt on the importance of hypericin alone. Up to two or three times that dose is likely to be entirely safe in most people, though above that threshold phototoxicity starts to become more and more likely.

Traditionally 1-4 ml of tincture are used three times daily. Tinctures of dried herb in 70% ethanol and moderately heated (to at most 80° C or 176° F) for 20 min leads to the best hypericin extraction, though the exact level of extraction was not reported (2). An infusion is made by adding 2 tsp dried herb to 1 cup boiling water and allowing to steep for 15-20 min. According to analyses of infusions made in 60-80° C (140-176° F) water there was extraction of at most 10% of the hypericin and 35% of the pseudohypericin from fresh herb (2).

Frontiers for future research include the exact, *in vivo* mechanisms of Hypericum and its many constitutents, comparison of crude and standardized extracts in clinical trials, and the effect of combining Hypericum with other mood-altering and centrally active botanicals and drugs. Some of this work is already underway, including two clinical trials showing a combination of Hypericum and *Valeriana officinalis* (valerian) to be more effective than amitriptyline (44) and desipramine (45). Safety data need to be obtained, particularly during pregnancy and lactation. This is because post-partum depression is a significant problem for many women and there is potential for applying Hypericum in mildly to moderately affected patients if it is safe.

Biography

Dr. Eric Yarnell received his naturopathic degree from Bastyr University, Seattle, WA in 1996. He now practices in Sedona, AZ and previously practiced in Denver, CO. He is a founding member and current secretary/treasurer of the board of the Botanical Medicine Academy, a specialty board for practitioners who use botanicals clinically. He writes a bimonthly piece on botanical medicine in *Alternative and Complementary Therapies*, is co-author of the *Phytotherapy Research Guide*, and a contributor to *The Natural Pharmacy*. He served as Letters Editor for the *Journal of Naturopathic Medicine*, Vol. 8, No. 1, and will be Research Editor starting with Vol. 8, No. 2.

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TABLE 1
PROPOSED ANTIDEPRESSANT ACTIONS OF HYPERICUM AND ITS CONSTITUENTS

Proposed Mechanism	Responsible Constituents	Problems	Reference(s)
MAO inhibition	hypericin	inhibitory activity extremely low	19, 20
MAO inhibition	flavonoids (e.g., campherol, luteolin, quercetin)	constituent levels too low for significant in vivo effect alone	20, 21
MAO inhibition	xanthones (e.g., tetra-hydroxyxanthone)	constituent levels too low for significant in vivo effect alone	20, 21
COMT inhibition	flavonoids	constituent levels too low for significant in vivo effect alone	21
serotonin reuptake inhibition	hypericin & crude extracts	concentrations used were higher than can be achieved in vivo for equivalent effect	22
suppression of serotonin receptor expression	hypericin	concentrations used were higher than can be achieved in vivo for equivalent effect	23
combined MAO inhibition, serotonin and norepinephrine reuptake inhibition	standardized extracts	not confirmed in vivo	24
elevation of melatonin levels	standardized extract	exact mechanism unclear	25
inhibit GABA binding to GABA-A receptors	hypericin & standardized extracts	not confirmed in vivo	2
suppress Il-6 secretion	standardized extracts	not confirmed in vivo	28

Abbreviations: COMT = catechol-o-methyltransferase, GABA = gamma-aminobutyric acid, Il-6 = interleukin 6, MAO = monoamine oxidase