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Hypericum in History: St. John's Wort

An inveterate member of many herbal pharmacopeias of cultures throughout the world, *Hypericum perforatum* has been used for over two thousand years to treat wounds, contusions, menstrual problems, hemorrhoids, and kidney stones(1). Pliny claimed it could cure the bite of poisonous snakes while early Christians used it to repel evil spirits through a pagan ritual of burning *Hypericum* on St. John's Eve (1). In contemporary herbalism *Hypericum perforatum* is referred to as St. John's wort, named in honor of John the Baptist by early Christians since it typically flowers around St. John's Day, the 24th of June (with "wort" being Old English for plant). However, it is perhaps best well known as a contemporary herbal treatment for depression with its popularity rapidly growing in Europe and the United States. Germany alone accounts for over 2.7 million prescriptions of St. John's wort (the most common being Jarsin(r)) making up more than 25% of all prescriptions in Germany for antidepressant drugs (2).

Increasing interest in the medicinal properties of St. John's wort has spawned many recent investigations into its clinical usefulness, its biological activity, and its chemical makeup. Such interest reflects a radical shift in how natural therapeutics and traditional medicines are regarded throughout the United States and Europe in the scientific and medical community as well as by the general public. Yet, since herbal therapeutics do not fall under the same regulations for efficacy, safety, and prescription as licensed drugs there is significant potential for false marketing, toxic side effects, and harmful drug interactions. Thus, to protect individuals as both consumers and patients scientific study is being fostered through the recent establishment of the NIH Office of Alternative Medicine, the "Guidelines for The Assessment of Herbal Medicines" released by the World Health Organization in 1992 as well as the establishment of institutes of alternative medicine in major research universities, including Harvard University and the University of Arizona. As the validity of many herbal therapeutics gains recognition and given the rising costs of health care the mainstream use of herbal treatments will continue to grow in importance as a component of health care.

What is Wort?

The taxonomy of *Hypericum perforatum* is debated. It is typically classified as either a member of the family Clusiaceae or the family Hypericaceae with the genus *Hypericum* consisting of over 370 species and 4 subspecies (3). Approximately 10 groups of bioactive natural constituents have been identified which may have pharmacological effects. These constituents include flavanoids, bioflavanoids, xanthones, and naphthodianthons, with the substances hypericin and pseudohypericin (members of the last family of compounds) being the agents suspected to have the most therapeutic activity (3). It is these later compounds that reside in the small black dots on all above-ground parts of *H. perforatum* that give *Hypericum* oil an intense red color and may also lead to phototoxicity upon ingestion of *H. perforatum* in some mammals (3).

The Biology of Depression

Over the past 10 to 15 years the pharmaceutical industry in Europe has started to develop standardized extracts of St. John's wort that have grown increasingly popular for treatment of mild to moderate depression. To understand how such extracts may act in depression as well as what side effects they may present we need to first explore current theories of depression. Depression is the most common major psychiatric disorder with over 15% of the population demonstrating a major depressive illness at some point in life (4). Standard criteria for depression include an abnormal sense of sadness and despair, disordered eating and weight control, diminished sexual interest, and abnormal sleeping patterns (5). Furthermore, depression can be classified as exogenous or endogenous, major or minor, and unipolar or bipolar depending on its time course, severity, and cyclicity if present. Evidence from twin studies suggests that many depressive illnesses demonstrate a genetic disposition although a precise etiology remain undefined. However, all major theories of depression address neurophysiological mechanisms as part of the cause of depressive illness.

At the synapse or junction between nerve cells neurotransmitters such as serotonin are released producing either excitatory or inhibitory input to the nerve cell's neighbor. The activity of neurotransmitters and neurotransmission is modulated through a variety of mechanisms including the synthesis and release of neurotransmitter, the catalytic breakdown of neurotransmitter following its release, the reuptake of the neurotransmitter by the nerve cell that released it or by its surrounding cells, and the diffusion of the neurotransmitter out of the synapse. More specifically, most antidepressant medications either decrease the uptake of a neurotransmitter (fluoxetine or Prozac and the tricyclic antidepressants), decrease the catalytic breakdown of neurotransmitters (monoamine oxidase inhibitors), and/or regulate the synthesis of neurotransmitter. Nearly all standard allopathic pharmacological treatments influence catecholaminergic and serotonergic neurotransmission suggesting that serotonin levels are important in giving an emotional timbre to thoughts and perception (1). Of the two, the serotonergic system seems to be the most heavily implicated system based on the clinical success of Prozac, a serotonin reuptake inhibitor, as well as findings in clinically depressed patients of decreased levels of serotonin metabolites in cerebrospinal fluid, decreased plasma tryptophan levels (the amino acid precursor to serotonin), and abnormalities in serotonin transport in platelets (4). Thus, production of serotonin (or 5-hydroxytryptamine) appears to be central for maintaining a positive affect as well as regulating some drives such as satiety, sexual interest, and the sleep-wake cycle (4). These findings are subsumed under the biogenic amine hypothesis of depression which implicates a deficiency in the regulation of serotonin and possibly norepinephrine as the biochemical etiology for most clinical unipolar depression. Nevertheless, several abnormalities remain to be explained, including dysregulation of the hypothalamic-pituitary neuroendocrine axis, alterations in circadian rhythmicity, decreased activity in the basal ganglia and frontal cortex, and altered noradrenergic activity in the cortex (4). For St. John's wort to act effectively as an antidepressant one would expect tropism in some of these systems as well as effects that resemble those of other proven antidepressants.

Hypericum Activity

Several studies indicate that *Hypericum* has substantial neurophysiological activity in brain areas important in depression with two primary hypotheses accounting for antidepressant activity. Cott has demonstrated high affinity of *Hypericum* for several receptors localized in the human cortex including NMDA, adenosine, GABAA, GABAB, monoamine oxidase A and B (MAO), benzodiazepine, and serotonin type 1 receptors(6). Furthermore, activity of the extract depends on several components, not simply the hypericin constituent which demonstrates strong affinity only for GABA receptors. Thus, one emerging hypothesis focuses on inhibition of MAO as the primary therapeutic action. Other researchers have failed to demonstrate similar affinities to monoamine oxidase (MAO); however, the failure to test for MAO activity with all constituents of the crude extract is the most likely culprit (7). Problems remain in that extract affinity for MAO has not been confirmed in vivo lending caution to the MAO hypothesis, although this may also reflect metabolism that is too rapid for a reliable assay of MAO activity.

A second line of evidence focuses more directly on the serotonergic system since *H. perforatum* extract has been found to inhibit serotonin uptake (7). Perovic and Muller found that *H. perforatum* extracts demonstrated a 50% inhibition of serotonin, lending strong support that St. John's wort may work similar to selective serotonin reuptake inhibitors (SSRI) and tricyclics (TCA) such as Prozac and Amitriptylin (7). Cott showed similar findings in his receptor assay but calculated that effects demonstrated by him and other investigators required levels of extract that are not likely to be achieved in therapeutic administration (7). Nevertheless, Muller et al. using similar levels demonstrated significant down-regulation of serotonin B-receptor and a significant up-regulation of serotonin receptors in the frontal cortex (8). These more recent findings have been replicated and show more consistency with the bioamine hypothesis although serotonergic and MAO activity may both be contributing to the therapeutic action of *H. perforatum* preparations.

Clinical Research

Perhaps the strongest lines of evidence validating St. John wort as an effective treatment for clinical depression can be found in several recent randomized clinical trials and meta-analyses. The popularity of St. John's for the treatment of depression in Europe has spawned considerable clinical research both comparing treatment of *H. perforatum* extract to placebo as well as to therapeutic doses of a variety of tricyclic antidepressants. Notably two recent meta-analyses have been presented in the literature compiling over 20 years of clinical research. Linde et al. investigated 23 randomized trials within the last ten years focusing on comparison of therapeutic administration of *H. perforatum* versus placebo and TCA treatment, using the self-reported Hamilton depression scale as an index of improvement and severity (9). The authors noted that *H. perforatum* extracts demonstrated significant improvement over placebo and a similar effectiveness to a therapeutic schedule of TCAs. A similar review by Volz of 12 placebo-controlled studies demonstrated a similar reduction in depressive symptomology between treatment groups with significant improvement over placebo (10). Both papers point to consistent methodological flaws in *H. perforatum* literature, including failure to adequately differentiate depressive groups by severity and type of depression, failure to investigate

treatment beyond 4 weeks, problems in standard use of the Hamilton depression scale, and potential problems regulating dosage of *H. perforatum*. However, two recent studies address the two former criticisms. First, Wheatley compared *H. perforatum* treatment with TCA treatment over 6 weeks among mild to moderately depressed patients and found that while both treatment groups demonstrated significant improvement over placebo, at 6 weeks treatment TCA showed a significant advantage (11). Second, Vorbach et al. investigated the antidepressant efficacy of St. John's wort extract versus TCA solely in severely depressed patients over 6 weeks and found significant although slightly impoverished effectiveness of St. John's wort over TCA, but with major advantages in tolerability (12).

Consistent throughout much of the review literature is that while *H. perforatum* treatment offers equivalent or marginally reduced effectiveness to that of TCA treatment, its side effect profile is much more tolerable with nearly half as many *H. perforatum* as TCA patients either complaining or dropping out (2). This is highly important in that number and severity of side effects determines compliance and thus the efficacy of a given treatment regime. Side effects to St. John's wort when present often include dry mouth and headache and uncommonly, gastrointestinal symptoms and fatigue; TCA treatment produces similar but more pronounced side effects with the addition of dizziness, nausea, and possible cardiovascular dysregulation. Furthermore, photosensitization is a possible side effect of St. John's wort although recent studies show this to be marginal (13). Notably, many drugs and food items can negate the therapeutic benefits of St. John's wort. Effective treatment requires eliminating one's intake of beer, coffee, wine, salami, yogurt, fava beans, smoked and pickled items, and chocolate - depressing in its own right! However, studies overwhelmingly indicate that a standardized extract from St. John's wort can be an effective alternative to typical antidepressants, with potentially fewer side effects. Issues still remain about how to standardize dosage and purity since, like many herbal therapies, *H. perforatum* does not have to meet the efficacy and purity standards of licensed drugs. Yet, like many other herbal therapeutics that are growing in popularity and in scientific interest, *H. perforatum* legitimizes alternative medicine and reflects an ethos of health that focuses more on habit, prevention, stress-reduction, and balance than more established allopathic medical regimens.

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