Herbal Medicines in the Treatment of Depression and Anxiety

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Abstract

Herbal medicines include a range of pharmacologically active compounds: in some cases it is not well understood which ingredients are important for a therapeutic effect. The supporters of herbal medicine believe that isolated ingredients in the majority of cases have weaker clinical effects than whole plant extract, a claim that would obviously require proof in each case. Although a multitude of pharmaceutical agents are available for the treatment of mental disorders, physicians find that many patients cannot tolerate the side effects, do not respond adequately, or eventually lose their response. In comparison, many therapeutic herbs have far fewer side effects. They can provide an alternative treatment or be used to enhance the effect of prescription medications. This review will indicate the quality of the evidence supporting the clinical effects of a number of commonly used types of herbal medicines for depression and anxiety.

Keywords: **Anxiety, Depression, Herbal medicine**

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Depression

Depression is a serious disorder in today's society. With estimates of lifetime prevalence as high as 21% of the general population in some developed countries. As defined by the American Psychiatric Association, depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioral and physiological levels. Such patients are often reluctant to take synthetic antidepressants in their appropriate doses due to their anticipated side effects including inability to drive a car, dry mouth, constipation and sexual dysfunction. As a therapeutic alternative, effective herbal drugs may offer advantages in terms of safety and tolerability, possibly also improving patient compliance [1]. The advent of the first antidepressants- the Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants (TCAs) in the 1950s and 1960s represented a dramatic leap forward in the clinical management of depression. The subsequent development of the Selective Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine in the past decade and a half has greatly enhanced the treatment of depression by offering patients medications that are as effective as the older agents but are generally more tolerable and safer in an overdose. The introduction of atypical antidepressants, such as bupropion, nefazadone, and mirtazapine, has added substantially to the available pharmacopoeia for depression. Nonetheless, rates of remission tend to be low and the risk of relapse and recurrence remains high. Thus, there is a need for more effective and less toxic agents [1]. Plants extracts are some of the most attractive sources of new drugs, and have been shown to produce promising results for the treatment of depression [2].

Hypericum perforatum L. (St. John's Wort)

As one of the best-studied botanicals of all time, St. John's wort (SJW) is notable for its ability to treat mild-to-moderate depression and is also known to be safe and effective for children. As a result, SJW has become very popular in the U.S., where it is available over the counter. In Germany, physicians prescribe SJW to patients with mild-to-moderate depression [3, 4]. The possible action of SJW stems in part from its hypericin and hypericin-like constituents, which may act on acetylcholinesterase by decreasing the degradation rate of acetylcholine. Sedative actions come from the hypericins, biflavones, and hyperforin. Other reports demonstrate a serotonergic activity, by which it can act as a weak serotonin-reuptake inhibitor (SSRI) that leads to fewer side effects. In addition, sigma 1 receptors, which are affected by antidepressant medications in animal studies, may also be affected by SJW. Most likely, the demonstrated efficacy of this botanical in treating depression is through its synergistic effects, orchestrated by the multitude of components in the whole herb working both within and peripheral to the central nervous system [5, 6, 7, 8].

A meta-analysis of 23 randomized trials which included 1757 outpatients with mainly mild or moderately severe depressive symptoms found that *Hypericum* extracts were significantly superior to placebo and similarly effective as standard antidepressants. Side effects occurred in 19.8% patients on *Hypericum* and 52.8% patients on standard antidepressants, and data analysis revealed a dropout rate of 0.8% for SJW and 3.0% for standard antidepressant drugs due to side effects [3, 4]. The action of SJW has been well characterized in direct comparisons with leading antidepressant medications. In a

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randomized controlled double-blind trial, 70 patients suffering from mild-to-moderate depression received one tablet of either SJW extract or fluoxetine twice a day for 6 weeks. Patients were rated by the 17-item Hamilton Rating Scale for Depression (HAMD) and the von Zerssen depression scale (ZDS). HAMD scores significant decreased ($p < 0.001$) in the SJW group (50%) and in the fluoxetine group (58%), and ZDS also decreased in both treatments (42% and 52%, respectively). Assessments by physicians and patients indicated considerable improvement with no between-treatment differences. The conclusion of that study is that SJW was therapeutically equivalent to fluoxetine and is therefore a reasonable alternative to synthetic antidepressants. *Hypericum* extract has similarly been tested and showed an efficacy similar to that of sertraline in the treatment of mild-to-moderate depression in a small group of outpatients. Efficacy and tolerability of SJW was also compared with imipramine and was equivalent to that of the drug in treating mild-to-moderate depression. In addition, patients tolerated SJW better than imipramine [3, 4]. In a review of over 3000 depressed patients spanning 34 double-blind trials, the effective dosage level of SJW for mild-to-moderate depression was between 500 and 1000 mg of standardized alcohol extract per day [4]. For patients with preexisting conductive heart dysfunction or elderly patients, high-dose *Hypericum* extract has been found to be safer with respect to cardiac function than tricyclic antidepressants. The side-effect profile of SJW extract is minor, especially when compared to the well known side effects of antidepressant medications. Due to its lack of monoamine oxidase (MAO) inhibition, SJW is not considered to interact negatively with MAO-inhibiting drugs or tyramine-containing foods. However, it has been shown that important SJW–drug interactions may occur. SJW can reduce the circulating levels of certain drugs. Synergistic therapeutic effects may also lead to complications and unfavorable treatment outcome. SJW is a potent inducer of cytochrome P450 (CYP) enzymes, particularly CYP 3A4 and/or P-glycoprotein, and it may also inhibit or induce other CYPs [9]. Although SJW induces photosensitivity in some patients, this not likely to happen with standard dosages; it has occurred mainly in HIV patients using larger than normal quantities for an antiviral effect. SJW is not recommended for use during pregnancy, because its safety in pregnancy has not been studied [9].

Lavandula angustifolia Mill. (lavender)

Lavender is used principally as an aromatic essential oil for relaxation. In a single-blind randomized control trial, 80 women who took daily baths with lavender oil experienced improved mood, reduced aggression, and a more positive outlook [2]. Furthermore, the combination of lavender (60 drops/day of a lavandula tincture) and imipramine (100 mg/day) was found to be more effective in the treatment of depression than either treatment alone, according to a double-blind randomized control trial. The findings of this study suggested that taking a moderate amount of lavender may help reduce the amount of tricyclic antidepressants needed to treat depression, leading to fewer side effects [2].

Crocus sativus L. (Saffron)

Saffron is the world's most expensive spice and apart from its traditional value as a food additive recent studies indicate its potential as an anti cancer agent and memory enhancer [10, 11, 12]. The value of saffron (dried stigmas of *Crocus sativus* L.) is

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determined by the existence of three main secondary metabolites: crocin and its derivatives which are responsible for color; picrocrocin, responsible for taste; and safranal responsible for odor. This plant belongs to the Iridaceae family and as a therapeutically plant, saffron it is considered an excellent aid for stomach ailments and an antispasmodic, helps digestion and increases appetite. It is also relieves renal colic, reduces stomach ache and relieves tension [10, 13]. Saffron is used for depression in Persian traditional medicine. [14]. Indeed, it is a Persian herb with a history as long as the Persian Empire itself. Iran, the world's largest producer of saffron has been investing in research into saffron's potential medicinal uses. Much of the work surrounds its traditional application for alleviating depression. The clinical findings suggest that saffron is a safe and effective antidepressant. For example, in a randomized, double-blind study, 30 mg of saffron extract (in capsules) given for 6 weeks resulted in significant alleviation of depression compared to those on placebo, and did so without evident side effects. This study was a follow-up to a preliminary trial in which the same saffron preparation performed as well as imipramine for treating depression in a double-blind trial. In further preliminary work, saffron was compared to the drug fluoxetine; it was found that saffron performed as well as the drug in the treatment of depression. [14, 15, 16].

Anxiety

Generalized Anxiety Disorder (GAD) is the most common anxiety disorder but being generally less severe than panic disorder. GAD is probably the disorder most often found with a coexisting mental disorder, usually another anxiety disorder or a mood disorder. The ration of women to men is about 2 to 1. The cause of GAD is not known. The primary symptoms of GAD are anxiety, motor tension, autonomic hyperactivity and cognitive vigilance. DSM-IV employs the following criteria for GAD: excessive anxiety and worry, occurring more days than not for at least 6 months, about a number of events or activities that are difficult to control [17]. Autonomic symptoms are no longer required for diagnosis. The principal neurotransmitter systems thought to modify anxiety are the gamma-aminobutyric acid (GABA) system, and the noradrenergic, serotonergic, dopaminergic and histaminergic system. The most effective treatment of patients with GAD is probably one of that combines psychotherapeutic, pharmacotherapeutic and supportive approaches. Because of the long-term nature of the disorder, a treatment plan must be carefully thought out. The two major drugs to be considered for the treatment of GAD are buspirone and the benzodiazepines. Benzodiazepines are the drugs most frequently prescribed for the treatment of anxiety disorders. They act through the benzodiazepines-GABA receptor, where they inhibit neuronal activity by increasing the chloride ion influx into neuron. This includes hyperpolarization of the nerve cell, a condition that leads to decreased responsiveness to incoming stimuli [17]. Several problems are associated with the use of benzodiazepines (BZDs) in GAD. About 25 to 30% of all patients fail to respond, and tolerance and dependence may occur. Some patients also experience impaired alertness while taking the drugs. In addition, there are several reports that indicate cognition impairment induced by benzodiazepines. The cessation of use of benzodiazepines can induce a withdrawal syndrome, characterized by: psychological symptoms of anxiety such as apprehension and irritability, physiological symptoms of anxiety such as tremor and palpitation and perceptual disturbances such as hypersensivity to light,

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sounds, touch or motion. Only one third of patients who have GAD seek psychiatric treatment. Many patients go to general practioners, internists, cardiologists and also use herbal medicine like passiflora [17].

***Passiflora incarnate* L.**

Passionflower (*Passiflora incarnata*) is a woody, hairy, climbing vine and is reputed to have sedative/anxiolytic properties and has been used widely as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture. The commission E approved the internal use of passionflower for nervous restlessness and the British Herbal Compendium indicates its use for sleep disorders, restlessness, nervous stress, and anxiety. A double blind and randomized trial showed that that passiflora extract is an effective drug for the management of generalized anxiety disorder and the low incidence of impairment of job performance with passiflora extract compared to oxazepam is an advantage [17].

Kava

Kava is a ceremonial and social drink in the South Pacific, containing approximately 250 mg of kava lactones. Its use is constrained by elaborate rituals in Fiji, Samoa, and Tonga where it has also been used for analgesia. Kava contains alpha-pyrones, a recently discovered class of potent skeletal muscle relaxants. In Germany, doses of 70 – 80 mg kava lactones are given t. i. d. for stress and muscle spasm. For milder symptoms, a dose of 60 – 70 mg kava lactones q.d. is usually sufficient. When six of the nine major alpha-pyrones found in Kava extract are administered together in animal studies, they create a synergistic effect. Whether or not Kava affects benzodiazepine or GABA-A receptors is controversial. However, it has anticonvulsant properties in animal models. Kava exerts some serotonin blocking activity and sodium channel blocking. In preclinical studies, the primary calming effect is mediated through the amygdale [18, 19, 20]. Kava's traditional use as an analgesic was confirmed in preclinical studies. Naloxone, when administered in doses that blocked morphine-induced analgesia, did not reverse Kava's antinociceptive effects. The intriguing finding that the analgesia induced by Kava occurs via non-opiate pathways deserves further study. Some double-blind, placebo-controlled studies support the efficacy of Kava for anxiety [21]. In patients with generalized anxiety disorder, Kava worked as well as oxazepam without producing any cognitive dysfunction. "Menopause related" anxiety in 20 women improved on kava by week 1 compared with no improvement in 20 women on placebo. Anxious patients receiving 70 mg kava lactones t.i.d. improved compared to a placebo group by week 1 and became increasingly better over 28 days, as measured by Hamilton Anxiety ratings, CGI, and self-ratings, with no side-effects reported. In the longest study to date, 108 patients were randomized to 70 mg kava lactones t.i.d. or to placebo. By week 25, Hamilton Anxiety scores dropped from 31 to 10 in the 59 patients on kava and fell from 30 to 15 in the 49 patients on placebo; 75% of the kava group attained significant global improvement with no evidence of dependency compared to 50% in the placebo group. Although the patients had clinically significant anxiety, this study, like the Lehmann et al. [19] study, suffered from lack of precise diagnoses. Recent reviews concluded that kava extract is relatively safe and more effective than placebo. Only three of the studies met criteria for meta-analysis, including the selection of patients by HAM-A >19 and treatment with kava extract WS1490 100 mg

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t.i.d. (210 kavapyrones/ day). Because of methodological questions in the studies, the authors suggested more rigorous risk-benefit trials [18, 19, 20]. Dosage and side effects: Two postmarketing studies of over 3,000 patients found a 1.5% and a 2.3% incidence of side effects. Gastrointestinal complaints, allergic skin reaction, headache, and photosensitivity were the most common side effects. Other complaints included restlessness, drowsiness, lack of energy, and tremor. Schelosky et al. described 4 cases in which kava induced symptoms suggestive of central dopaminergic antagonism, including dystonic reactions (eyes, neck, and trunk), oral/lingual dyskinesias, and one case of worsening Parkinsonian symptoms in a woman on levodopa [22]. Until more information is available, kava should be avoided in patients with Parkinson's disease and in those at risk for dystonia or dyskinesia. No studies of long-term safety, teratogenicity, or mutagenicity beyond 6 months have been done. Kava should not be combined with alcohol or other sedatives [18, 19, 20].

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