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The effect of most important medicinal plants on two important psychiatric disorders (anxiety and depression)—a review

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ABSTRACT

Anxiety and depression are highly comorbid psychiatric conditions that the prevalence will be increased to the second greatest risk of morbidity, causing a significant socioeconomic burden. Due to side effects and destructive effects of some chemical drugs, many patients prefer herbal medicines to treat diseases. Although there are key review papers in the area of medicinal plants and psychiatry disorders, they have either covered the area in a relatively cursory manner or focused on a specific plant medicine. In the present study, we tried to present the effect of most important medicinal plants on two important highly comorbid psychiatric conditions—anxiety and depression.

1. Introduction

Stress, anxiety and depression are of prevalent and highly comorbid psychiatric conditions in the world, which are defined as a negative emotional experience and associated with biochemical, cognitive, behavioral and psychological changes. Herbal medicine has been widely used among sufferers of mood and anxiety disorders since antiquity^[1,2].

Depression is a common, chronic and recurring disorder with some properties like low cognitive and emotional reactions that imposes high expenses to patients and remedial system^[3]. Chronic and recurring nature of depression has changed it to a resistant disorder against treatment^[4]. Depression is a common disorder with prevalence of about 15% during the lifecycle, and today it is considered as the main reason of disability around the world and is in the fourth rank among ten main

reasons of world load of diseases. It is predicted that after cardiovascular disease, depression prevalence will be increased to the second greatest risk of morbidity, causing a significant socioeconomic burden^[5].

Anxiety is resonant situation of emotional stimulation that contains the fear or worry feeling. Unlike the patients with fear, the patients with worry feeling often understand danger source vaguely. Studies show that among the behavioral problems, anxiety has the highest frequency, and studying factors affecting students' anxiety demonstrates that physical factors, factors related to growth periods, social, family and affective factors have significant effect on their anxiety^[6]. About 500 million individuals in the world suffer from anxiety disorder^[7]. Anxiety has various mental and physical signs including palpitation, cramp, perspire, asthma, nausea, provocation, urination, feeling of fear and stress, failure to encounter position, uncertainty about future, expectation of sorrow occurrence, inability of concentration and night sleeplessness^[8].

Due to side effects and destructive effects of some chemical drugs, many patients prefer herbal medicines

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to treat diseases^[1]. From a sample size of more than 2000 subjects interviewed during 1997–1998, it was estimated that more than half of those suffered anxiety attacks, and more than 54% of those with severe depression had used medicinal plants or other complementary therapies during the previous 12 months to treat their disorders. The inpatients hospitalized for acute care of various psychiatric disorders in North America also showed that 44% had used herbal medicines during the previous 12 months for psychiatric purposes^[9].

About 25% of all drugs prescribed by doctors in the current medicine are obtained from herbs in different forms. Some of them are produced directly from plant extracts and others are produced artificially to provide effects similar to herbal drugs^[10].

Over the last two centuries, with the isolation of active constituents, such as morphine from opium poppies, recognition of psychoactive plants has significantly advanced^[1], and various kinds of researches on herbal medicine have increased in recent years with more than 50% increase in the literature over 5 years up to 2008^[11].

Although not all commonly used phytomedicines are safe, most of herbal products available as “over-the-counter” psychotropic medicines are fairly safe, with fewer adverse effects in comparison to conventional drugs such as antidepressants^[12,13]. Furthermore, in some cases research in medicinal plants resulted in discovery of highly effective drugs such as development of opiate anesthetics, aspirin, digitoxin and taxol^[14]. Many medicinal plants have been recognized for the treatment of specific disorders, but some of them are grown in some specific areas and are used for thousands of years without being entered in books or recognized by scientists. Therefore, in the present study, we tried to present the effect of most important medicinal plants on two important highly comorbid psychiatric conditions—anxiety and depression. Although there are key review papers in the area of medicinal plants and psychiatry disorders, either have they covered the area in a relatively cursory manner or focused on a specific plant medicine such as *Hypericum perforatum* (*H. perforatum*)^[15]. While research is increasing in the area of herbal psychopharmacology to date, no comprehensive review exists exploring the use of botanicals in the treatment of depression and anxiety disorders. These are highly comorbid, and as psychotropic herbal medicines exert an array of psychopharmacological actions.

A search was done on electronic databases such as Web

of Science, MEDLINE (PubMed), Cochrane Library, CINAHL and Google Scholar to review the evidence of herbal medicines with antidepressant and anxiolytic activities. Databases were searched for both *in vivo* and *in vitro* data on major herbal medicines used commonly in psychotherapy, using the search terms of “anxiety” or “depression” combined with the search terms “medicinal plants” or “botanical medicine” or “herbal medicine”, in addition to hand-searching the literature.

2. Pathogenesis of depression

In the last decades, the pathogenesis of depression has focused on monoamine impairment, lowering of monoamine production, or secondary messenger dysfunction^[16]. In recent years, added attention has also focused on the role of neuro-endocrinological abnormalities such as cortisol excess, as well as cytokine or steroidal alterations, changes in GABAergic and/or glutamatergic transmission, impaired endogenous opioid function, and abnormal circadian rhythm^[16,17].

3. Pathogenesis of anxiety

The pathophysiology of anxiety is not as clear as depression and still needs to be established. However, current evidence indicates that the pathophysiology of anxiety includes neurobiology abnormalities of noradrenergic, serotonergic, GABAergic and glutamatergic transmission^[18]. Involvement of these systems is reflected in the efficacy of benzodiazepines, selective serotonin reuptake inhibitors as well as selective serotonin and noradrenalin reuptake inhibitors in the treatment of anxiety^[19].

4. Mechanism of action herbal medicines

The antidepressant mechanisms of action of herbal medicines, in most cases, are not as clear as with synthetic drugs, having a multitude of biological effects on reuptake and receptor binding of various monoamines, commonly in addition to endocrine and psychoneuroimmunological modulation^[20]. Some medicinal plants with antidepressant activity such as *H. perforatum*, *Crocus sativus* (saffron)

(*C. sativus*) and *Rhodiola rosea* (*R. rosea*) (roseroot), offer promising results for the treatment of depression via known psychopharmacological actions such as inhibition of monoamine re-uptake (noradrenaline, serotonin and dopamine), monoamine oxidase inhibition, sensitization and enhancement of serotonin receptors binding, or neuroendocrine modulation[20]. Other suggested effects include GABAergic effects, opioid and cannabinoid system effects[21].

Some herbal medicines, such as *R. rosea* and *C. sativus*, with mood elevating effects also display anxiolytic activity. This may be due to modulation of neurological pathways (GABAergic, serotonergic, and noradrenergic systems) that have both antidepressant and anxiolytic effects. This may also be due to inter-relation effects. Hence, following depression treatment, anxiety may also be reduced[22].

Several herbal medicines have shown antidepressant activity in preclinical and clinical trials. The most important of these, having clinical trials, are detailed in Table 1 and the others which mostly have preclinical trials along with their components are summarized in Table 2.

In a recent meta-analysis of randomized controlled trials, compared with selective serotonin reuptake inhibitors,

H. perforatum yielded a significant difference in favor of *H. perforatum* over conventional antidepressants for withdrawal. A recent study involving 426 responders which were assessed for remission rates after continuation of 26 weeks consumption of 300 mg *H. perforatum*, three times a day, or placebo, revealed a relapse rate for completers of 18% compared to 26% for placebo.

The tolerability of *H. perforatum* has been shown to be better than some synthetic antidepressants. Comparative studies between *H. perforatum* extract and paroxetine, revealed 10 to 39 fold higher adverse events rate for paroxetine. It should be noted that high-dose of hyperforin extracts (10 mg/d) causes CYP3A induction, however, 4 mg/d of hyperforin extracts showed no significant effect on this enzyme[62].

Two trials using 60 mg–90 mg of *C. sativus* extract showed significant improvement of depression over placebo[63]. Equivalent effects occurred in three clinical trials comparing *C. sativus* with imipramine and fluoxetine[64].

These results seem to be encouraging, however, the shortage of trials lengths (4–6 weeks), smallness of sample sizes ($n=30-45$) are limitations which exist in confirming the efficacy potential of these compounds.

Table 1

Mechanisms of action and clinical applications of herbal antidepressants.

| Plants | Effects and possible mechanisms | Clinical use | Major active component | Reference |
|---------------------------------------|--|---|------------------------------------|-----------|
| <i>Echium amoenum</i> (borage) | Antidepressant, anxiolytic effects (unknown mechanism) | Anxiety depression | Rosmarinic acid Thesimine | [23] |
| <i>C. sativus</i> (saffron) | Dopamine, norepinephrine, serotonin reuptake inhibition GABA agonist NMDA receptor antagonism Anxiolytic effects | Anxiety depression | Safranal | [24–26] |
| <i>H. perforatum</i> (St John's wort) | Dopaminergic activity Serotonin, dopamine, norepinephrine re-uptake inhibition Decreased degradation of neurochemicals Increased binding/sensitivity to 5-HT _{1A,B} Glutamate neuronal release inhibition Neuroendocrine modulation Anti-depressant and anxiolytic activity | Depression Bipolar depression | Hyperforin Hypericin | [27–29] |
| <i>Lavandula</i> spp. (lavender) | GABA modulation | Anxiety depression Somatic tension | Linalool Linanyl acetate | [30–32] |
| <i>Panax ginseng</i> (Korean ginseng) | HPA-axis modulation Dopamine, norepinephrine and serotonin modulation Anti-inflammatory and antioxidant activities Inhibition of nitric oxide synthesis | Depression Poor cognition Fatigue | Ginsenoside Rb1 Ginsenoside Rg1 | [33,34] |
| <i>Albizia julibrissin</i> (mimosa) | 5-HT _{1a} and 5-HT _{2c} receptor binding affinity Antidepressant, anxiolytic effects Decreases sleep latency and increases sleep duration) | Anxiety Depression Insomnia | Julibroside | [35,36] |
| <i>R. rosea</i> (roseroot) | Monoamine oxidase A inhibition Monoamine modulation (5-HT) Anti-anxiety Inhibition of cortisol release, stress-induced protein kinases, nitric oxide | Anxiety depression Fatigue Cognition impairment | Rosavin | [37–39] |

Table 2

Anxiolytic and antidepressant plants and their components.

| Scientific name | Family name | Biologic substances | Reference |
|--|------------------|---|-----------|
| <i>Achillea millefolium</i> | Asteraceae | Essential oil, polyphenolic compounds, some species of flavons, sesquiterpene, lactones, betaine, acetylene compounds, resin, tannin, achillion, phosphate, nitrate, potassium salts, organic acids | [40] |
| <i>Cassia fistula</i> | Fabaceae | Sterols, flavonoids, anthraquinones, diterpenoids, three terpenoid, catechin, furfural, chrysophanol | [41] |
| <i>Citrus aurantium</i> | Rutaceae | Hesperidin, neohesperidin, doxepin, apigenin | [42] |
| <i>C. sativus</i> L. | Iridaceae | Crocine, crocetin, picrocrocin, safranal | [43] |
| <i>Dracocephalu polychaetum bornum</i> | Lamiaceae | Terpene, tannin and phenolic acids, geraniol, geranyl acetate, noural and rosmarinic and caffeic acids, cinnamic acid derivations, tannin and three terpenes like oleanolic acid and acacetin | [44] |
| <i>Foeniculum vulgare</i> | Apiaceae | Palmitic acid, oleic acid, linolenic acid, petroselinic acid | [45] |
| <i>Humulus lupulus</i> | Cannabaceae | Humulus (HOPS) | [46] |
| <i>Lavandula angustifolia</i> Mill. | Labiatae | Linalool acetate, linalil-acetat, sinoel, nerol, perneol, camarines, tannins, flavonoids | [47] |
| <i>Matricaria chamomilla</i> | Asteraceae | Terpenoid oil essences (azlon, chamazulene, oxide flavonoids), bisabolol, a and b sesquiterpenes (apigenin, chrysen, luteolin, quercetin), coumarins (umbelliferone), cycloserine and mucilages, salts, polysaccharides, tannin and fatty acids | [48] |
| <i>M. officinalis</i> | Lamiaceae | Citral, geraniol, linalool, citronellal, caffeic acid, anethole, terpineol-4, carvacrol-4, piperitone, eugenol, acid rosemary, phenolic acids and flavonoid, camosic acid, linoleic acid, ursolic acid, rosmarinic acid | [49] |
| <i>Mentha piperita</i> | Lamiaceae | Acetaldehyde, amyl alcohol, menthyl esters, pinene, phellandrene, cadinen, pulegone, dimethyl sulfide, alpha-pinene, sabinene, ocimene, gama-terpinen, citronellol | [44] |
| <i>Nardostachys jatamansi</i> | Valerianaceae | Isovaleric, valepotriate, sesquiterpenes acid | [50] |
| <i>Ocimum basilicum</i> | Lamiaceae | Thujone, myrcene, linalool, geraniol caryophyllene, carrone, ursolic acid, apigenin, farnesol fenchone-pinene, cis-ocimene, trans-ocimene, camphor, eugenol, methyl-eugenol, alpha-farnese, alpha-bisabolene, D-germacrene, cineole | [51] |
| <i>P. incarnata</i> | Passifloraceae | Vitexin, iso-vitexin, passiflorin, harman, limonene, cumene, alpha-pinene | [50] |
| <i>Peganum harmala</i> | Nitrariaceae | Norharmalin, harmin, harmaline and harmal | [51] |
| <i>Primula vulgaris</i> | Primulaceae | Gamma-linolenic, linolenic acid | [52] |
| <i>Prunus amygdalus</i> | Rosaceae | a-Linolenic acid, eicosapentaenoic acid, oleic acid and docosahexaenoic acid | [53] |
| <i>Rosa</i> spp. | Rosaceae | Geraniol, citronellol, linalool, stearoptene | [54] |
| <i>Scrophularia striata</i> | Scrophulariaceae | Phenolic, flavonoid and flavonolic compounds, cinnamic acid, isorhamnetin-3-o-rutinoside, quercetin, phenylpropanoid glycoside, nepitrin, acteoside | [55] |
| <i>Silybum marianum</i> L. | Asteraceae | Cilimarine | [56] |
| <i>Spinacia oleracea</i> | Amaranthaceae | Acid linoleic, aid palmetic folic acid, saponin, lecithin, hexa acid linoleic, carotene, lycopene, coumaric acid, nucleoside purine, rubiscolin | [57] |
| <i>Stachys lavandulifolia</i> | Laminacea | Phenylethanol, terpenoid, flavonoid, myrcene, alpha-pinene, gamma-murolene | [58] |
| <i>Tilia platyphyllos</i> Scop. | Tiliaceae | Different flavonoids like tiliroside, quercetin, isoquercetin, hyperoside and different amino acids like alanine, cysteine and cystine | [59] |
| <i>Vitex agnus</i> | Verbenaceae | Phytoestrogen | [60] |
| <i>Vitex agnus-castus</i> | Verbenaceae | Sabinene, pinene, sesquiterpene, chrysophanol, aucubin | [61] |

Passiflora incarnata: *P. incarnata*; *Melissa officinalis*: *M. officinalis*.

C. sativus is also a promising antidepressant. However, there is only one clinical evaluating *Echium amoenum* in the treatment of depression. Results revealed that the herb was superior to placebo in reducing depression four weeks after drug consumption, with no significant anxiolytic activity[65].

A clinical trial comparing *Lavandula* spp. with imipramine and the combination revealed that *Lavandula officinalis* was not as effective as imipramine, and their combination was more effective than imipramine alone, indicating a possible synergistic effect.

A three-arm study using 340 mg/d and 680 mg/d *R. rosea* extract, in comparison to placebo in the treatment of mild-moderate depression revealed a significant dose-dependent

improvement in drug groups compared with placebo[66].

5. Clinical trials for anxiety

Several plants with anxiolytic activity have been studied in clinical trials. A meta-analysis review of seven randomized controlled trial papers using *Piper methysticum* (*P. methysticum*) showed a significant reduction in comparison to placebo control group[67]. Another study on *P. methysticum* revealed a similar results, however, there are other studies showing no positive results[68–70].

A clinical trial revealed that acute administration of *Scutellaria lateriflora* attenuated anxiety[71]. A pilot clinical

trial revealed equivocal efficacy to oxazepam (30 mg/d) *P. incanata* extract in reduction of anxiety, with neglectable side effects[72].

An acute study using *P. incanata* for pre-surgical anxiety showed a significant reduction of anxiety. Toxicological study of *P. incanata* also revealed no evidence of safety concerns with this herb[73].

A clinical trial using a flexible dose of *Matricaria recutita* revealed a significant effect in favour of the plant intervention, with no significant adverse effects in *Matricaria recutita* group, even with higher doses[74]. *Ginkgo biloba* (ginkgo) extract (480 mg/d or 240 mg/d) in patients with anxiety, also revealed a significant dose-dependent reduction[75].

H. perforatum has been shown to reduce anxiety in long term drug usage, with low level of side effects[76].

In social phobia, a clinical trial exists using *H. perforatum* with flexible-dose of 600–1800 mg, in which no significant difference was found with placebo[78].

Many anxiolytic plants reviewed had potential applications. These include improvement in mood (*P. methysticum* and *M. officinalis*), reduction in muscle tension or pain *Eschscholzia californica* (*E. californica*), hypnotic or sedative action for insomnia (*Scutellaria lateriflora* and *P. incanata*), or enhancement in cognition [*Ginkgo biloba* and *Bacopa monniera* (*B. monniera*)]^[21]. However, while the results are positive for a large group of medicinal plants, no definitive conclusion can be reached in some cases, as anxiety condition is notorious for high placebo response, and in some studies, no placebo arm has been employed.

6. Discussion

There are growing preclinical and clinical trials, which show beneficial efficacy for herbal medicine to treat anxiety and depression. However, concerns exist over poor reporting of data in some clinical trials. The other issue is that many herbal medicines have not yet been rigorously tested in human clinical trials. Several herbal medicines such as *B. monniera*, *E. californica*, *M. officinalis* and *Withania somnifera*, mimosa (*Albizia julibrissin*), *Zizyphus jujuba*, *M. officinalis* and *E. californica* have been researched in preclinical models with positive results, however, these have not been yet studied as monotherapies in the treatment of psychiatric disorders. It should be noted that plants constituents undergo significant metabolism,

being biotransformed into new chemical structures. Thus *in vitro* evidence cannot always be extrapolated to clinical efficacy in humans. Therefore, in this study we tried to mostly present clinical evidence of efficacies.

It should be noted that some medicinal plants reviewed in this paper other than being used in modern practice to treat anxiety and depression, are used for other complex conditions. For example, *E. californica* is used for insomnia and pain^[79], *B. monniera* for treatment of cognitive deficits^[80], and *M. officinalis* for gastrointestinal complaints such as dyspepsia^[81].

The difference in bioequivalence of preparations used in the clinical trials should be taken in consideration. This matter is important when the results of different clinical studies are not consistent.

Clinical or preclinical evaluation of medicinal plants is a complicated task. For example, the chemical composition of herbal preparations depends on many factors, such as environmental and genetic differences, harvest time, exposure to airborne vectors, soil quality, differences in plant parts used, and preparation methods. Consequently, it is difficult to produce standardized extracts with reproducible chemical composition. While preclinical studies of main active constituents are helpful, the evidence cannot guarantee the same efficacy of total extract in replicated batches^[82].

It should be noted that stress is not considered as disorder, but when stressors are continuous over a period of time, anxiety and depression can arise affecting largely on mood. The stress causes abnormal accumulation of free radicals which are the key factors in induction of various complications such as diabetes^[83,84], atherosclerosis^[85,86], cardiovascular diseases^[87,88], neurological disorders^[89,90] and cancer^[91,92], other than anxiety and depression. These conditions may cause many changes, including alterations in redox state^[93,94].

It has been revealed that stressed individuals have less levels of antioxidants in their blood serum than those who were not suffering from anxiety or depression.

Furthermore, the supplementation with vitamins high in antioxidants (A, C, and E) has had a positive impact on severity of symptoms reported. Therefore, each of the plants reviewed here has its own mechanism of action, however, most of medicinal plants possess antioxidant activity^[95–98]. Medicinal plants have been shown to alleviate stress induced diseases such as diabetes^[99,100], cancer^[101,102], infection^[103,104] and gastrointestinal disorders^[105,106].

Therefore, their effects on anxiety and depression, at least in part, might be due to their antioxidant activities.

In conclusion, while medicinal plants reviewed in this paper are encouraging for the treatment of anxiety and depression, further research utilizing robust methodology, the use of biotechnologies to ensure bioequivalence of product and good manufacturing practice is still required to promote more confidence.

Conflict of interest statement

We declare that we have no conflict of interest.

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