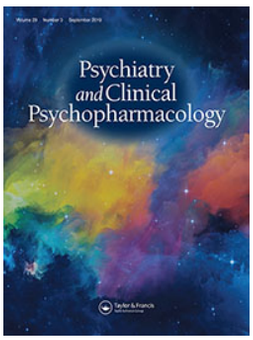

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INVITED ARTICLE

Level of clinical evidence of herbal complementary therapies in psychiatric disorders

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Psychiatric diseases including depression, anxiety, schizophrenia, and insomnia are common mental health problems with high economic and social costs. Especially, major depressive disorder which is one of the top five most predominant diseases worldwide has been estimated to affect the majority of the world's population with great impact on the quality of life of a person by causing headache, difficulty in thinking, and loss of interest. Currently, although number of treatments such as psychotherapy, electroconvulsive therapy and antidepressant drugs are available for these patients safety concerns, side effects (libido, dry mouth, and constipation), limited efficacy and low tolerability are important issues in clinical practice. Huge number of studies have shown the relationship between the foods the person takes and the manner the person acts. Therefore, mood fluctuations and psychiatric disorders are found to be associated with diet and certain aspects are evaluated as complementary therapy approaches especially in resistant cases. Recent findings clearly showed that increased intakes of red meat, high-fat foods, and refined sugars and/or reduced intake of fresh fruit, vegetables, grains and fish seems to be critical. Increasing evidence support the idea that Mediterranean diet via the gut microbiota-brain axis has definitely an impact on protection in depression. Besides, there is considerable epidemiological evidence to indicate that a diet rich in fish has a lower incidence of depression and EPA 1 g/day is an effective strategy for augmenting antidepressants' effects in resistant cases. EPA has a capacity to suppress inflammatory states which can reduce acute phase protein C-reactive protein and pro-inflammatory cytokines. On the other hand, it is well known that fermented foods have benefits on mental health indicating Psychobiotics especially bifidobacteria and Lactobacillus acidophilus have an antidepressant potential by reducing corticosterone levels and proinflammatory cytokines. These prebiotics are fibres metabolized by the microbiota and capable of increasing the levels of good bacteria such as bifidobacteria can reduce cortisol response which is strongly linked to anxiety and depression. It is also considered that high fibre diets can reduce symptoms of depression [1–5].

Plant-based products are becoming progressively mainstream. This is not simply a comment on their popularity, but on the level of scientific research and acceptance by clinical researchers as well as the attention being paid to therapeutic options by specialists. For several years in the past, the quality of studies involving herbal products and other alternative treatment options for psychiatric and other disorders has been criticized. Criticisms have included failing to account for biases and confounders, using non-standardized products and poor research design. However, in the last 5 years, MEDLINE (www.ncbi.nlm.nih.gov/PubMed) has indexed several randomized handled trial offers investigating complementary medicines for treating mental disorders, suggesting that the increasing number of option approaches are being examined using what is the future approach of treatment. There are several natural remedies for depression and anxiety such as passion flower, lemon balm, valerian, chamomile, Californian Poppy, oats, hawthorn, wild lettuce wood betony, brahmi, catnip, hops, boldo, vervain, Siberian ginseng, rosemary, peppermint, mullein, Jamaican dog wood, cramp bark, *Ginkgo biloba*, St Johns wort, lavender oil, scull cap, lime flower (Linden Blossom), mother wort, damiana, gotu kola, etc. In this editorial, some plant species which are commonly found in Turkey and/or Mediterranean region with clinical effectiveness are reviewed [6–9].

Crocus sativus L. (Saffron): Saffron, which is mainly a plant of Western Asia, is cultivated and often used in traditional medicine in the Mediterranean region of Turkey and also in Iran, Israel, Italy, Greece, and Egypt. Major active components are cirocin (30%), picrocrocin (5–15%) and, other volatile compounds (5%) containing safranal which has therapeutic value in mood disorders. Especially saffron has a therapeutic value on cognitive dysfunctions. Clinical studies have also shown saffron to be an effective antidepressant.

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Thus, in a 6-week RTC study it was shown that *C. sativus* (a capsule/30 mg/day) improved mild depression via producing a significantly better outcome on the Hamilton depression rating scale compared to placebo [10]. In another preliminary double-blind and randomized study, Saffron (at 30 mg/day or 15 mg bid dose) was found to be effective similar to fluoxetine (at 20 mg/day or 10 mg bid dose) in the treatment of mild to moderate depression for 6 and 8-weeks, respectively [11,12]. In a double-blind randomized clinical trial study after taken the hydroalcoholic extract of *C. sativus* (40 or 80 mg) and fluoxetine (30 mg/ day) for 6 weeks, it has been reported that *C. sativus* 80 mg plus fluoxetine was found to be more effective than that of *C. sativus* 40 mg and fluoxetine to treat mild to moderate depression [13]. In a double-blind study patients with Alzheimer(AD), after taking a capsule of saffron 30 mg/day (15 mg twice/day) or donepezil 10 mg/day (5 mg twice/day), it has been observed that, this dose of saffron had similar effects compared to donepezil in the treatment of mild-to-moderate AD. Therefore, this II stage study suggests that saffron extract has a possible therapeutic effect in the treatment of patients with mild to moderate Alzheimer's disease. In a supporting study patients with AD ($n = 46$) who were treated with saffron have been shown to have better cognitive functions than those treated with placebo [14].

Hypericum perforatum L. (*St John's worth*): *H. perforatum*, commonly known as St John's wort (SJW), is a herbal remedy that has been used to treat emotional distress since the end of the 15th century. Hypericin (0.3–0.5%), hyperforin (3.0%) and various flavonoids are found in the content of the plant. In recent years, it is the first-line treatment option in the treatment of major depressive disorders in certain European countries. *H. perforatum* has an affinity for receptors of numerous neurochemical systems. In a comparative 27 clinical trials with 3808 depressive patients, St John's wort and SSRI were compared and St John's wort demonstrated comparable responses and remission rate like SSRIs with lower clinical side effects in ameliorating depressive symptoms [15]. Similarly, in another meta-analysis study *H. perforatum* was found as effective as SSRI in depressive cases and authors suggested that, these effects were limited as the treating time with extract (from 4–12 weeks period) and long-term efficacy and safety of *Hypericum* extract remain to be examined [16]. In a mechanistic study with 23 participants (13 patients and 10 controls with major depressive disorder), it has been emphasized that St John's worth has no effect on MAO-A [17]. There are also other studies showing the effectiveness of *H. perforatum* in the treatment of obsessive compulsive disorder, social anxiety disorder and anxiety [16,18,19].

Camellia sinensis (L.) Kuntze (Tea): This plant is the ancient green tea prepared as a beverage across the world as well as Turkey and has many beneficial effects on human health. Black tea has numerous components including flavonoids (Thearubigins (TRs) and theaflavins (TFs) and catechins), phenolic acids, methylxanthines (caffeine), theanine, β-carotene, folate, vitamins C/K. Polyphenols, epigallocatechin, epigallocatechin gallate, epicatechin gallate, and epicatechin are the major catechins present in green tea. Since some differrences occur during the tea processing, catechins biotransformation classifies; the green (non-oxidized), the black (totally oxidized), and oolong (semi-oxidized) and also white tea. In a study with 26 subjects (a double-blind, randomized, placebo-controlled design) it has been shown that tea is a relevant contributor to our daily cognitive functioning. L-theanine (L-γ-glutamylethylamide) is an amino acid contained in green tea (*C. sinensis*). In a study, patients with major depressive disorder it has been suggested that chronic (8-weeks) l-theanine administration is safe and has several beneficial effects on depressive symptoms, anxiety, sleep disturbance, and cognitive impairments. L-theanine crosses the blood–brain barrier. There is modest evidence about the improving effects of black tea consumption on mental alertness, planning capacity and concentration in work while reducing the short- and long-term memory impairments [20].

Lavandula angustifolia Mill. (Lavender): Lavender is a small, fragrant shrub native to the Western Mediterranean Region, Southern France, Italy, Arabian Peninsula, Spain, and Greece. *L. angustifolia* (syn. *L. officinalis*) is one of the major medicinal plants used in the treatment of central nervous system disorders including anxiety, stress and sleep disorders in pharmacy and aromatherapy. Studies reveal that *Lavandula* has high content of linalool and linalyl acetate (chemical constituents). Potential antidepressant activity of *Lavandula* and its effect on a variety of neurotransmitters which involve in pathophysiology of depression of *Lavandula* is currently unknown. On the other hand, it has been reported that basic anxiolytic effects of lavender is based on its major components especially linalool. In general, lavender oil is used in perfumery and cosmetics industry, as well as in soap fragrances. Nowadays, in aromatherapy, some essential oils are known as anxiolytic through oral use, inhalation and massage application. Lavender is one of the best-selling natural ingredients, especially as an essential oil. The inhalation of linalool odor, a major component of *L. angustifolia*, has been shown to have a sedative effect on both humans and animals [21]. In an another study conducted with 122 patients who admitted to the general intensive care unit, reported that they felt less anxious and more positive immediately after lavender aromatherapy, and also increased the effectiveness of other treatments [22]. In a randomized trial with 80 patients with major

depression were assigned into two groups of experimental treatment group and standard treatment group and the first group, has only been given Citalopram 20 mg and the second group took 2 cups of the infusion of 5 g dried *Lavandula angustifilia* in addition to Citalopram 20 mg twice a day. The patients were followed up for 4–8 weeks. *L. angustifolia* infusion had some positive therapeutic effects on depressed patients, decreased mean depression score, and at the same time it has been stated that it might be used alone or as a supplement to some anti-depressant drugs [23]. In a randomized, placebo-controlled trial investigating the anxiolytic effect of Silexan (a patented active substance with an essential oil produced from *L. angustifolia*), it has been found that it had a pronounced calming and anxiolytic effect in patients suffering from restlessness associated with anxiety and sleep disturbance [15]. In an another randomized placebo-controlled trial held by Effati-Daryani et al., it was shown that anxiety, stress and depression in pregnant women could be improved by using Lavender cream [24].

Passiflora edulis Sims (Passion flower): The genus *Passiflora* consists of 500 species in worldwide and this plant has been used widely as herbal medicine in West India, Mexico, The Netherlands, South America and Italy. Bioactive constituents are aminoacids, beta carbolin alkaloids and flavonoids especially chrysin. In some clinical trials, *P. edulis* has major effects for the treatment of some diseases such as anxiety, opiates withdrawal, insomnia, attention-deficit hyperactivity disorder (ADHD) [25]. A double-blind RCT (36 patients with generalized anxiety disorder) suggests that Passiflora extract is an effective herbal medicine for the management of generalized anxiety disorder (with reduced mean Hamilton Anxiety Rating Scale), and exhibits low incidence of impairment of job performance compared to oxazepam [26]. In a randomized-clinical trial with 63 patients administration of Passion flower extract as a sedative agent during periodontal treatment has been revealed to be significantly effective in reducing anxiety [27]. In another randomized clinical trial, *P. edulis* (260 mg) or midazolam (15 mg) were orally administered to 40 dental surgery patients (before surgery). Result of the study showed that passiflora has an anxiolytic effect similar to midazolam in adult patients and discussed to be safe and effective for conscious sedation [28]. In a double-blind and placebo-controlled study held by Aslanargun et al., it was demonstrated that oral administration of *P. edulis* suppresses the increase in anxiety before spinal anesthesia without changing psychomotor function test results [29]. In Belgium, a traditional herbal medicinal product (200 mg dry extract per coated tablet) is used to relieve the mild symptoms of mental stress, such as nervousness, worrying or irritability and to aid sleep in adults and children from age 12.

Melissa officinalis L. (Lemon Balm): Lemon Balm is one of the medicinal plants (grown in a wide geography) of Mediterranean region and it is cultivated in Europe. It is consumed as tea prepared from its leaves and has a lemon-like aroma. *M. officinalis* has a role as a traditional medicinal plant in psychiatry because of its mild sedative effect [30]. In a double-blind, placebo-controlled study, after 4 weeks of treatment with *M. officinalis* essential oil aromatherapy had a positive effect on the agitation and quality of life of 71 patients with severe dementia [31]. In a double-blind, placebo-controlled, randomized, crossover study ($n = 18$ healthy volunteers) cognitive performance was assessed by Defined Intensity Stressor Simulation (DISS) test at two doses of *M. officinalis* extract (300, 600 mg). When the results were compared, 600-mg dose of *M. officinalis* showed a significant increase in self-rated calmness and reduced alertness in subjects [32]. A combination of valerian and lemon balm extracts used in a study with 900 children revealed satisfactory results in the treatment of restlessness and sleep disturbances [33]. Seven weeks treatment with valerian and lemon balm mixture in primary school children with restlessness, concentration difficulties and impulsiveness ($n = 169$) caused a reduction in symptoms and problems in both school and at home. Hyperactivity, concentration difficulties and impulsiveness improved during seven weeks' treatment with valerian root and lemon balm extracts in primary school children [34]. According to a double-blind placebo-controlled clinical trial, in patients with chronic stable angina use of 3 g *M. officinalis* (8-week) decreased depression, anxiety, stress, and sleep disorder compared with the placebo group [35].

Treatment discontinuation of well-established remedies often occurs due to side effects of pharmacological agents, and poor gain access to and bias against mental interventions prevent wider subscriber base of the interventions. Several contributory therapies now have adequately high-quality evidence to consider their use. Clinicians enthusiastic about further information on supporting therapies should turn to one of a variety of reliable sources. Given the highly prevalent use of complementary therapies for mental health complaints among patients, clinicians should become more mindful of the benefits and harms of herbal complementary therapies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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