Herbal medicines and botanicals for managing insomnia, stress, anxiety, and depression: A critical review of the emerging evidence focusing on the Middle East and Africa

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ARTICLE INFO

ABSTRACT

Background: Mental health issues affect millions of people globally, imposing significant emotional and economic burdens. These involve multiple pathogenic mechanisms, including oxidative stress and neuroinflammation. With an annual global death estimated at 9 million, neurological disorders are the second leading cause of death. This review aims to explore the benefits of 15 medicinal plants available within MEA and provide researchers with knowledge on how these herbal medicines could alleviate symptoms associated with changes in mental health.
Method: Academic databases were searched to find relevant studies on traditional medicinal herbs used in the MEA for the treatment of mental health related issues like sleep, anxiety and depression.
Result: The MEA region has the highest prevalence of major depressive and anxiety disorders globally, with conventional treatments often involving medications that alter neurotransmitters, potentially leading to adverse effects. Given the concerns about long-term drug use, there is growing interest in multi-targeted approaches using medicinal plants. These offer a cost-effective, less hazardous alternative, especially for those with chronic, comorbid conditions. Medicinal plant-based food supplements are increasing within the MEA region, where cultural and traditional usage of such plants is extensive. However, the practical application of these supplements is often limited in real-world scenarios.
Conclusion: While medicinal plant-based food supplements show potential as a cost-effective and a more suitable alternative for individuals with chronic and comorbid conditions in the MEA region, further research is needed to overcome the limitations in their practical application including a focus on real world data.

1. Introduction

Mental health disorders manifest as a spectrum of syndromes that cause progressively deteriorating neural tissue, including cognitive decline and motor dysfunction, arising from various pathogenic mechanisms like oxidative stress, calcium instability, and neuroinflammation [1–4]. These disorders intersect with mental health issues such as anxiety and mood disorders, affecting clinical outcomes and quality of life. Anxiety and mood disorders are the primary mental conditions associated with other mental health disorders impacting their clinical progression, treatment response, clinical outcomes, and overall quality of life. A number of pain disorders have been associated with anxiety and strategies to evade fear [5].

Mental health disorders pose significant emotional and economic burdens globally, affecting millions in terms of anxiety, sleep issues, cognitive and memory function decline or dementia [6]. The global prevalence of mental disorders in 2019 was 16,983 cases per 100,000 population [7]. Surveys around the world showed that annual incidence rates of mental health disorders are estimated to be 10–15 per 100,000, 2 % of which are people over the age of 65 years. According to a 2019

estimate, approximately 50 million individuals worldwide had mental disorders resulting in memory loss. This number is expected to rise to 152 million by 2060 [8]. According to recent data in 2021 from 204 countries, the highest prevalence of major depressive and anxiety disorders was found in the MEA region [9].

Anxiety and depression often co-exist with other diseases. The conventional treatments used for anxiety and depression involve medications that alter neurotransmitters, leading to potential adverse effects [10]. To treat chronic conditions like anxiety, depression, insomnia, memory loss, etc., long-term drug use is inevitable. Given the concerns about the long-term use of conventional treatments, there is growing interest in multi-targeted approaches to treat these chronic conditions, including traditional, complementary and integrative medicines (TCIM e.g., medicinal plants). These offer a cost-effective and less hazardous alternative, especially for those with chronic conditions [10]. Serious side effects from synthetic anti-depressants and anxiolytics include headaches, sexual dysfunction, addiction, seizures, and suicide. As evidenced from a systematic literature review, these side effects were reduced in 45 % of the studies, where herbal medicines were used for the same indications [11].

Since ancient times, herbal medicines have been used to treat neurological symptoms. The World Health Organization (WHO) reported that 80 % of the world's population relies on traditional medicine (medicinal plants) for general health. In countries like Ghana, Mali, Zambia, and Nigeria, the use of herbal medicine is the first line of treatment for 60 % of children with high fever resulting from malaria [12]. Herbal medicines are widely used and recommended in Middle Eastern countries like Jordan for general health [13]. Similarly, in many other countries, there are many resources for self-treatment. For example, in Ghana, about 70 % of the population depends primarily on traditional medicine for mental health care [14]. About 27 million South Africans use TM for variety of aliments including management of symptoms mimicking mental health disorders [15]. Makundi EA et al., 2006 found that traditional health care has contributed significantly to the treatment of convulsions in rural Tanzania [16]. In some instances, patients use traditional medicine simultaneously with modern medicine to alleviate sufferings associated with disease and illness [17].

Medicinal plants are widely used due to their availability, accessibility, affordability, and perceived safety relative to modern medicine. Incorporating plant-derived compounds in standard care can enhance the efficacy of conventional treatments. Today a great number of modern drugs are still derived from natural sources, and ~25 % of all prescriptions contain one or more active ingredients from plants. [18]. While the pharmacology of these medicinal plants is not known, some of them have anti-inflammatory or antioxidant properties that can influence the peripheral system [19]. Studies also show that up to 35 % of people who have a disease use herbal supplements and that people with chronic diseases use herbal supplements more than people who don't have these diseases [20].

Traditional practices in South Africa and the Mediterranean region leverage plant resources for integrated health maintenance. Traditional healing practices in the MEA region have long recognized the therapeutic potential of plants in promoting neurological health, with a diverse range of medicinal plants used to address neurological disorders. Many studies have confirmed the neuroprotective activity of certain native medicinal plants in the MEA region [18,21–26]. In many African countries, including Nigeria, herbal medicine is well embraced, as up to 90 % of rural dwellers rely on it for their primary health care [19]. For instance, in Iranian traditional medicine, *Crocus sativus* L. is used to treat cognitive disorders. Ashwagandha (*Withania somnifera*(L.) Dunal), found within the Middle East and parts of Africa, is used in Unani medicine as it has gained recognition in treating anxiety, stress, and various health conditions. Ashwagandha is also categorized as an anti-inflammatory agent and one of the most prominent traditional medicines for treating certain neurodegenerative diseases [27].

This review explores the potential benefits of utilizing traditional medicinal practices and plant-based remedies, specifically in the MEA region. By focusing on this specific region, the review aims to shed light on the rich herbal knowledge and practices passed down through generations in MEA. It focuses on showcasing the effectiveness of traditional medicinal plants and their compounds found to alleviate symptoms associated with insomnia, stress, anxiety, and depression.

2. Methodology

We conducted a comprehensive search of academic databases such as Medline, Embase, Google Scholar, and ScienceDirect to identify relevant studies on the traditional medicinal plants used in the MEA region for the treatment of mental health issues. The keyword combinations of the following basic and Medical Subject Headings terms were used: "mental health," "sleep," "insomnia," OR "depression," "mental care," "mental condition," "mental state," "psychic health," "biologic stress," "physiologic stress," "stress," "stress reaction," "physiological stress," "ethnomedical plant," "ethnomedicinal plant," "medical plant," OR "Phytomedical plant," "phytomedicinal plant," "Phyto-therapeutic plant," "medicinal plant," and "Middle East and Africa region".

3. Mental health issues or symptoms mimicking mental health disorders

Mental health disorders are a broad category of diseases that affect the nervous system, including the brain, spinal cord, and peripheral nerves. These disorders can arise due to the factors such as genetic mutations, infections, trauma, stress, or autoimmune responses [28]. This review focuses on neuropsychiatric issues, specifically addressing mood disorders such as depression and anxiety, sleep disturbances, and related cognitive function decline. The scope includes discussions on memory impairment within these contexts but does not extend to neurological diseases like Alzheimer's and Parkinson's.

3.1. Stress, anxiety, depression and insomnia

One of the most common triggers for mental health disorders is stress. Stress is a natural response our bodies experience when encountering challenging or demanding situations [29]. It triggers a complex response involving the sympathetic–adrenal–medullary (SAM) and hypothalamic–pituitary–adrenal (HPA) systems [30–32]. When an individual encounters stress, the hypothalamus activates the "fight or flight" response via the SAM system. This leads to rapid physiological changes, including increased heart rate, blood pressure, and glucose levels, facilitating quick reactions [10]. Globally, stress affects more than 75 % of adults regularly, with variations among countries and individuals due to factors like work, finances, relationships, and societal expectations. Chronic stress disrupts the body's natural balance, leading to persistent anxiety and fear. It also impacts the HPA axis and central norepinephrine system, potentially contributing to depression, as the prolonged activation of the "fight or flight" response can cause neuronal changes [29,33]. Beyond the "flight-or-fight" response to acute stress, there are events in daily life that produce a type of chronic stress and lead over time to wear and tear on the body ("allostatic load"). Yet, hormones associated with stress protect the body in the short-run and promote adaptation ("allostasis"). A brief description of this mechanism is presented in Fig. 1 below.

As per a WHO 2019 report, anxiety disorders affect 301 million people globally, making them the most common psychiatric condition [34,35]. Anxiety can lead to work and school absences and results in a larger cost burden than other psychiatric disorders due to its higher prevalence. A review of epidemiological and clinical studies investigated quality of life in patients with panic disorder, social phobia, posttraumatic stress disorder, generalized anxiety disorder (GAD), and obsessive-compulsive disorder. The results described among persons with panic disorder in the community, 35 % felt they were in fair or poor
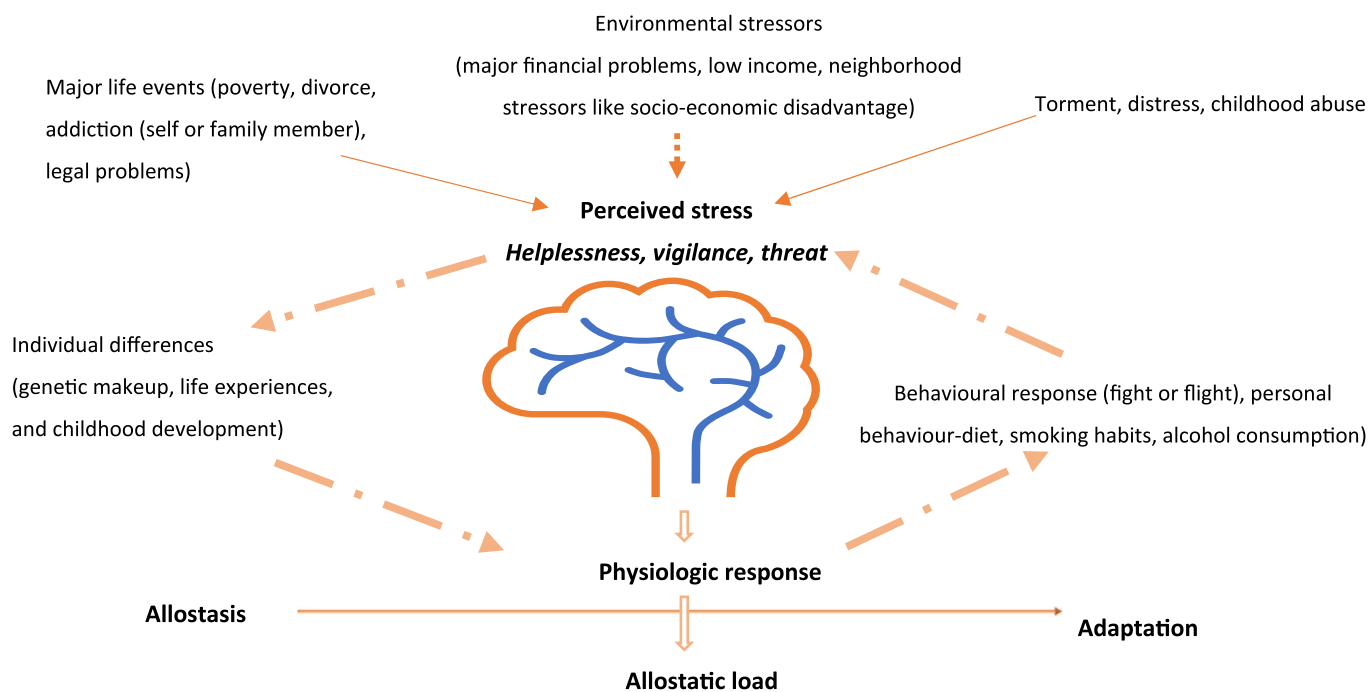
Figure 1 content:

Environmental stressors (major financial problems, low income, neighborhood stressors like socio-economic disadvantage)

Major life events (poverty, divorce, addiction (self or family member), legal problems)

Torment, distress, childhood abuse

Perceived stress
Helplessness, vigilance, threat

Individual differences (genetic makeup, life experiences, and childhood development)

Behavioural response (fight or flight), personal behaviour-diet, smoking habits, alcohol consumption)

Physiologic response

Allostasis → **Adaptation**

Allostatic load

Fig. 1. Mechanism of how body's natural balance is disturbed in chronic stress.

physical health, and 38 % felt they were in poor emotional health. Anxiety, encompass various disorders characterized by excessive worry, often co-occurring with depression and other mood disorders [36–38].

Depression affects 280 million individuals globally, including 23 million children (WHO 2019), sharing genetic and symptomatic traits with anxiety disorders [34,35]. According to a cross-sectional study by Kugbey N in 2018 [39], 37.8 % of the geriatric population (≥ 65 years) in Ghana suffered from depression. Based on the intensity of depression, this prevalence consisted of 23.3 % mild depression, 9.2 % moderate depression and 5.3 % severe depression [39]. Depression is linked to deficiencies in monoaminergic transmitters, while mania is associated with neurotransmitter excess [33]. Brain-derived neurotrophic factor (BDNF), a neurotropic factor, and serotonin (5-hydroxytryptamine, 5-HT) influence neurogenesis and synaptic plasticity [40], while animal models suggest dopamine system alterations in depression. Dopaminergic mesolimbic and mesocortical systems are involved in hedonia and motivation, two core symptoms of depression. The negative correlation between tissue content and extracellular DA in the accumbens may suggest a decreased cell-firing in the ventral tegmental area (VTA). The absolute refractory period of VTA dopaminergic neurons is 2.5 ms [41].

People who have anxiety and depression suffer from insomnia and are at a heightened risk of suicide, suicidal thoughts, and non-suicidal self-injury. Sleep disturbances are reported among up to 90 % of patients with major depressive disorder (MDD). There is evidence for a bidirectional association between insomnia and MDD [42]. It is a prevalent sleep disorder, affecting 5 %-15 % of the global population, with chronicity observed in 31 %-75 % of cases [43]. It is characterized by difficulties falling asleep, nocturnal awakenings, and early morning waking. Genetics and behavioural factors, such as stress and maladaptive coping, contribute to hyperarousal and insomnia, which are linked to increased adrenocorticotropic hormone (ACTH), cortisol release, and dysregulation of the sleep-wake switch [44,45]. Norepinephrine, dopamine, and 5-HT promote wakefulness, while gamma-aminobutyric acid (GABA) induces sleepiness [44]. Glutamate/GABA signalling is crucial for sleep-wake cycles, with interleukin-1β (IL-1β) and tumour necrosis factor (TNF-α) affecting glutamatergic activity [46]. Sedative-hypnotic drugs impacting GABAergic function are associated with depression, anxiety, and sleep disorders [47–49].

4. Mechanism

4.1. Mechanisms related to inflammation

TNF-α and interferon-gamma (IFN-γ) are pro-inflammatory mediators during acute brain inflammation and immunosuppressive over time. Its primary sources are microglia, astrocytes, and neurons during neuroinflammation [50]. TNF-α plays a role in homeostasis regulation, synaptic plasticity, learning, memory, and sleep/wake cycles. High levels are linked to neuroinflammation and neurodegenerative diseases. Neurodegenerative disorders, synaptic impairment, and neuronal mortality are all influenced by neuroinflammation, which is exclusive to the central nervous system. A strong correlation exists between this inflammation and oxidative stress (OS), as reactive oxygen species released by inflammatory cells initiate OS [51].

4.2. Mechanisms related to oxidative stress

Oxidative stress initiates inflammatory responses by generating pro-inflammatory cytokines and the expression of adhesion molecules, favouring cerebral issues (e.g., oedema and platelet aggregation) [51]. It plays a critical role in neuroinflammation and neurodegeneration, making early anti-oxidative treatments a potential avenue for intervention [52]. A detailed mechanism is given in Fig. 2.

Traditional systems of medicine practiced for thousands of years recommend using herbal therapies to aid memory and cognition [53]. *Rosmarinus officinalis* L. (Rosemary) is used to manage insomnia, while *Melissa officinalis* L. is used to manage anxiety and depression. Moreover, natural products like curcumin, resveratrol, and green tea extract show promise in mitigating these conditions [54]. Medicinal plant-based products can be considered as supplementary drugs for their positive influence on both anxiety and depression [55–58].
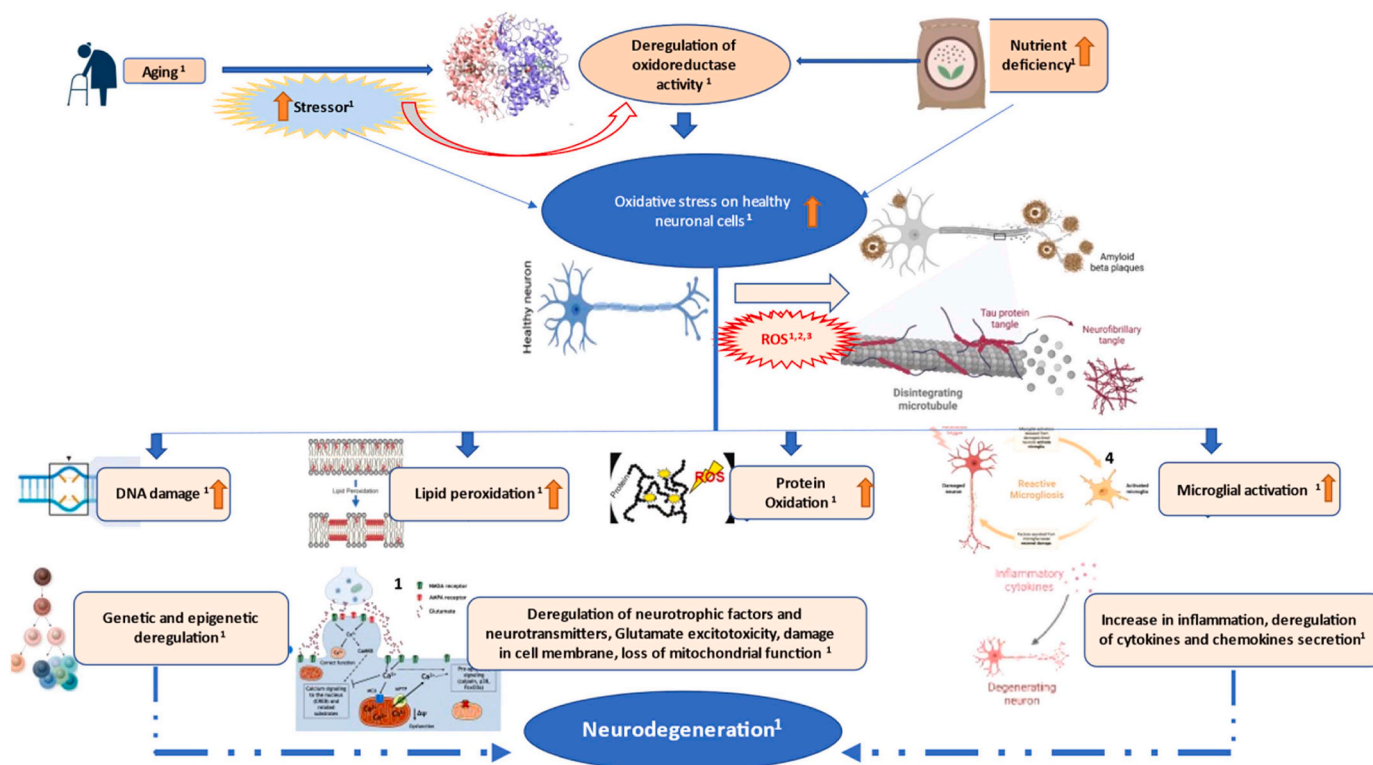
Fig. 2. Effect of oxidative stress due to several stressors on neurodegeneration.

5. Plants used in the management of mental health related issues like sleep, stress, anxiety and depression

The MEA region is host to a wide array of medicinal flora and takes pride in the longstanding cultural use of plants, used as a part of TCIM, as exhibited by the several published works on the ethnobotanical use of such herbal medicines [4,51,59–71]. A list of medicinal plants is provided in the Table 1.

5.1. Bacopa monnieri (L.) Wettst

B. monnieri (Plantaginaceae), a perennial medicinal plant native to tropical and subtropical regions, including Africa and the Middle East, is utilized in Ayurvedic medicine for conditions like mental stress and memory loss [72]. It contains active metabolites such as herpestine, d-mannitol, hersaponin, saponins, bacopasides, bacosaponins, alkaloids, polyphenols and monnierin, which are implicated in neuronal synthesis and synaptic activity and contribute to its neuroprotective effect [72, 73].

B. monnieri has demonstrated multi-targeted neuroprotection, including modulation of heat shock proteins (Hsp70) and cytochrome P450 activity in the rat's cerebrum, enhancing cellular resilience against neurotoxicity [74]. Uabundit et al. [75] demonstrated protective effects of *Bacopa monnieri* extract (BME) in male Wistar rat model that had been induced with 2 nmol/2 μL ethylcholine aziridinium ion (AF64A). Results showed that 20, 40, and 80 mg/kg BW of BME was able to mitigate the memory impairment and neurodegeneration in the rats by enhancing the escape latency time ($p<0.01$) in the Morris water maze test. They also observed that both cholinergic neuron and neuron density reduction were lessened [75]. It protects against glutamate toxicity induced by 5 mM glutamate in *Caenorhabditis elegans* (*C. elegans*) and modulates glutamate receptor binding and N-methyl-D-aspartate (NMDA) R1 gene expression in hippocampus of temporal lobe epileptic rats [76,77]. Long-term administration of *B. monnieri* (200 mg/kg orally per day for three months) significantly reduced pro-inflammatory cytokines in rat brain [73]. It also acts as an acetylcholinesterase (AChE) inhibitor, suggesting its utility in cognitive dysfunction [78].

Clinical trials using KeenMind®, an ethanolic extract of *B. monnieri*, showed cognitive improvements without affecting anxiety. Post-hoc probing using a paired-sample t-test revealed that the change from baseline to 2 h post-administration was significantly greater in the 320 mg condition than in the placebo condition [t (16) = 3.89, p=0.001]. The analysis of the change scores for calmness ratings indicated that no significant main effect of the condition was apparent. The analysis of state anxiety scores revealed a trend for the main effect of the condition [F(2,16) = 2.88, p=0.086] [79]. In another study, Bacopa significantly affected the delayed recall of word pairs task (F1,74 4.932, p<0.05). Follow-up analyses using analysis of variance (ANOVA) showed a significant reduction in performance between the last learning trial and the delayed recall test in all three testing sessions (F1,74 =6.035, p<0.05, F1,74 =12.256, p<0.01, and F1,74 = 18.830, p<0.01, respectively) [80]. A systematic review by Pase M et al., 2012 suggested that Bacopa improved performance on 9 of 17 tests in memory-free recall and could potentially be clinically prescribed as a memory enhancer [81].

5.2. Capparis spinosa L. (Caper)

C. spinosa (Capparaceae}, commonly known as Caper, is a perennial shrub native to the Mediterranean [82,83]. Diverse flavonoids, alkaloids, and phenolic acids exhibit antibacterial, antioxidant, and anti-cancer properties [84]. Alkaloids constitute 0.91 % and 0.86 % of the total mass in root bark and fruits, respectively, with abundant indoles [85].

Caper preparations have a potential in managing mental health conditions. Goel et al., 2016 [85] reported caper bud extract exhibits potential protective effect against learning and memory damage induced by chronic administration of lipopolysaccharide (LPS) (175 μg/kg) for 7 days, and the results suggest that the capers bud extract could be explored for its use in the treatment of cognitive issues

Table 1
List of various herbal medicinal plants found in the MEA region, their bioactive compounds, and pharmacological properties.

Plant Name (Family)	Origin/Native	Key metabolites	Therapeutic Uses & Effects	Research Findings & Clinical Trials	Reference
Sceletium tortuosum (L.) N.E.Br. (Kanna); Aizoaceae	South Africa	Mesembrine, mesembrenol, tortuosamine, and chennaine	Anti-depressant, anti-anxiety, cognitive enhancement	Inhibition of acetylcholinesterase (AChE) and Monoamine oxidase (MAO-B); potential in managing memory loss and cognition	[10,116, 147,148, 152]
Nigella sativa L. (Black cumin); Ranunculaceae	Arab regions, Asia, Africa	Thymoquinone	Anti-anxiety, memory enhancement, stress management	Animal trials show increased activity and reduced anxiety; human trials show stress and sleep management	[64,130, 132,133]
Withania somnifera (L.) Dunal (Ashwagandha); Solanaceae	Africa	Withanolides	Stress and anxiety management, immunomodulatory properties	Human trials show reduced anxiety assessments; limitations include small sample sizes	[109, 165–169]
Crocus sativus L. (Saffron); Iridaceae	Israel, Turkey, Iran, Egypt	Crocins, picrocrocin	Depression and anxiety alleviation	Clinical trials show reduced insomnia and improved cognitive subscale (ADAS-Cog) scores	[52,95–98, 100–103]
Bacopa monnieri (L.) Wettst.; Scrophulariaceae	Africa, Middle East	Bacosides, saponins	Neuroprotection, cognitive enhancement	Animal models show protection against neurotoxic insults; human trials show cognitive function improvement	[74,77–79, 81]
Mentha × *piperita* L. (Peppermint); Lamiaceae	Middle East	Menthol, menthone	Stress reduction, cognitive enhancement	RCT shows reduced anxiety and stress levels; other studies show improved alertness and memory	[121, 123–125]
Centella asiatica (L.) Urb. (Gotu kola); Apiaceae	Tropical and subtropical regions	Asiaticosides	Cognitive enhancement, anxiolytic properties	*In vitro* tests show reduced Reactive oxygen species (ROS); animal models show improved cognitive abilities	[89,91,93]
Rosmarinus officinalis L. (Rosemary); Lamiaceae	Middle Eastern countries	Carnosic acid, Carnosol, Rosmarinic acid, Ursolic acid	Neurological benefits, glycaemic management, antioxidant properties, and potential in patients with memory loss.	Clinical trials have shown cognitive improvement in memory loss patients.	[26,61,137, 138]
Vitis vinifera L. (Grape); Vitaceae	Iran, Iraq, Cyprus, Turkey	Anthocyanin mono-glucosides, Resveratrol, Quercetin, Catechin	Neuroprotective, anti-amyloid precursor protein, antioxidant, potential in memory loss diseases.	Limited clinical trials: however, animal studies show promise in neuroprotection.	[68,159, 161]
Capparis spinosa L. (Caper); Capparaceae	Mediterranean, Africa, Asia	Flavonoids, Alkaloids, Phenolic acids, Fatty acids, Glucosinolate derivatives	Neuroprotective, anti-inflammatory, cognitive improvement.	No clinical trials yet; research is primarily *in vitro* and animal studies.	[82–84,88]
Melissa officinalis L. (Lemon balm); Lamiaceae	Mediterranean, Western Asia	Rosmarinic acid, Volatile metabolites like geranial, neral, citronellal, geraniol	Cognitive improvement, mood enhancement, sleep quality improvement.	Clinical trials have shown significant improvement in sleep quality and mood enhancement.	[113,116, 119]
Salvia officinalis L. (Garden Sage); Labiatae/Lamiaceae	Middle Eastern, Mediterranean	Alkaloids, Carbohydrates, Fatty acids, Phenolic compounds	Cognitive improvement, anxiety reduction, potential in dementia, and other neurological problems.	Clinical trials have shown cognitive improvement and reduced anxiety in patients with memory loss.	[139,142, 144,145]
Valeriana officinalis L.; Caprifoliaceae	Iran, Turkey	Valepotriates, Valeric acid, Free amino acids like GABA	Sedative, hypnotic, anxiolytic effects, potential in GAD and insomnia.	Clinical trials have shown effectiveness in treating insomnia and GAD.	[70,154, 156,157]
Matricaria chamomilla L. (Chamomile); Asteraceae	Mediterranean region; Not Specified	Terpenoids, Phenolic compounds, Essential oils	Anxiolytic, anti-depressant, sleep quality improvement, potential in GAD and depression.	Clinical trials have shown effectiveness in treating anxiety and improving sleep quality.	[109–111]
Foeniculum vulgare Mill. (Fennel); Apiaceae	Mediterranean	Trans-anethole, Pinene, Fenchone	Anti-inflammatory, analgesic, antioxidant, potential in neurodegenerative disorders, stress alleviation, potential in depression.	Limited clinical trials: however, animal studies show anti-inflammatory and antioxidant effects.	[104,106, 107]

related to mental health. The study found that lipopolysaccharide treatment in animals led to a loss of acquisition and memory. When treated with *C. spinosa* extract, the time to reach the platform decreased significantly (p<0.001). LPS administration reduced positive alternations to 47 % of the control group. The administration of *C. spinosa* buds extract improved cognition, as evidenced by an increase in spontaneous alternation after and before LPS induced impairment in both pre- and post-treated groups (p<0.05) [85]. Turgut et al., 2015 [86] investigated the potential of *C. spinosa* seed extract in preventing DNA damage and cognitive impairment associated with Alzheimer's disease in BALB/c mice induced by D-galactose. The results showed that *C. spinosa* extract (200 mg/kg) daily for eight weeks provided significant protection against DNA damage and attenuated D-galactose-induced learning dysfunctions in mice as evident by spatial navigation task and probe task (p<0.01). Moreover, extract reduced the malondialdehyde (MDA) levels and increased activities of superoxide dismutase, glutathione peroxidase, and catalase levels in mice brain. The antioxidant activity of *C. spinosa* may partially contribute to the improvement of learning and memory function [86].

Mohebali, Shahzadeh Fazeli et al., 2018 [87] demonstrated Caper's effects in modulating inflammation-associated genes in a rodent model injected with amyloid-beta peptide, potentially due to its high flavonoid content. The effects of *C. spinosa* extract was observed on amyloid-beta peptide (Aβ)-injected in male Wistar Aβ-induced rats. After six weeks of oral administration, real-time quantitative polymerase chain reaction (qPCR) was conducted to determine the expression of amyloid precursor protein (APP), presenilin1 (PSEN1), and presenilin2 (PSEN2) genes in the hippocampus. The results showed a significant (p<0.021) down-regulation of APP, PSEN-1, and PSEN-2 genes compared to the control group [87]. *C. spinosa* mitigates oxidative stress induced by free radicals in multiple organs as evidenced in a study conducted by Mirzakhani N et al., 2020 [88] where the effects of the hydro-alcoholic extract of *C. spinosa* fruit, quercetin (Q), and vitamin E (Vit E) on monosodium glutamate (MSG)-induced toxicity in rats. Chronic administration of MSG resulted in decreased heart, kidney, and liver tissues activity of superoxide dismutase (SOD), which was normalized by high dose *C. spinosa* fruit extract and further improved by quercetin and vitamin E treatments. Specifically, the tissue SOD activity was 8.30 ± 1.08 U mg-1

protein after MSG administration and increased to 12.98 ± 1.35 U mg-1 protein with caper, quercetin, and vitamin E treatments. These findings suggest that *C. spinosa* fruit extract, quercetin, and vitamin E have potential antioxidant effects in reversing the negative impact of MSG on SOD activity [88].

5.3. Centella asiatica (L.) Urb. (Gotu kola)

C. asiatica (Apiaceae), or Gotu kola, a perennial medicinal native to tropical and subtropical regions of Asia, Africa, and Northern Australia, is used traditionally for its adaptogenic properties [89]. The plant contains triterpenoids like asiaticosides, asiatic acid, madecassoside, and madasiatic acid, demonstrating neuroprotective effects [90].

Gotu kola leaf extract enhances cognitive functions, including learning and memory, in rodent models through neurotransmitter modulation involving dopamine, 5-HT, and noradrenaline. Clinical trials have shown that Gotu kola extract improves working memory in humans with higher dosages [72]. The plant also has anxiolytic properties, beneficial for treating GAD [91–93]. It also serves as an alternative to AChE inhibitors, as highlighted in a systematic review by Puttarak P et al., 2017 [93] *C. asiatica* effectively improved the cognitive function of stroke patients. Patients were divided into three groups and administered 1000 mg/day, 750 mg/day of *C. asiatica* extract, and 3 mg/day of folic acid, respectively and treated at the acute phase of stroke infarction for six weeks. The Montreal Cognitive Assessment (MoCA-Ina) test was conducted at the beginning of treatment and after 6 weeks of therapy evaluated the patients' cognitive function. The 1000 mg/day treatment group scored highest among the three. The mean difference in score of MoCA-Ina at the 6th week vs in the beginning was 5.6 ± 4.61 (p<0.001; 95 % CI), 4.94 ± 2.16 (p<0.001; 95 % CI), and 4.06 ± 3.11 (p<0.001; 95 % CI) for the Gotu kola 1000 mg, 750 mg group, and 3 mg of folic acid [94].

5.4. Crocus sativus L. (Saffron)

C. sativus (Iridaceae), or saffron, is a perennial geophyte with a long medicinal history and growing recognition for its therapeutic potential in mental disorders. Bioactive metabolites such as safranal, picrocrocin, and crocin have been identified and are responsible for its effectiveness [52]. Saffron and crocin possess potent antioxidant activity and inhibit amyloid-beta aggregation, a hallmark of memory loss [52]. Based on a systematic review, *C. sativus* helps manage severe depression, and the benefits are likely attributable to the plant's serotonergic, antioxidant, anti-inflammatory, neuro-endocrine, and neuroprotective properties [95].

Various clinical trials, generally of lower quality, have also confirmed its benefits in stress management and insomnia. For instance, a randomized controlled trial with 431 participants showed improved sleep quality and reduced insomnia severity. *C. sativus* reduced insomnia severity (standard mean deviation (SMD): 0.53; 95 %CI: −0.05–1.11; I2 statistic = 59 %; p=0.08) and increased sleep quality (SMD 0.89, 95 % CI 0.10–1.68; I2 statistic = 90 %; p=0.03; 6 studies, 308 participants, very low-quality evidence) and duration (SMD: 0.57; 95 %CI: 0.21–0.93; I2 statistic = 40 %; p=0.002; 5 studies; 220 participants, moderate-quality evidence) as compared to placebo [96]. Additional extensive clinical trials are required to completely comprehend its mechanisms and therapeutic potential.

Therapeutic benefits of the stigma of *C. sativus* in the treatment of mild to moderate depression have also been suggested. At the end of the a trial, the ethanolic (80 %) extract of *C. sativus* stigma was found to be effective, like fluoxetine, in the treatment of mild to moderate depression (F=0.03, d.f.=1, p=0.84) [97]. Another phase II study provides preliminary evidence that administration of ethanolic extract of saffron stigma as a capsule 30 mg/day (15 mg twice daily) was as effective as donepezil for treating mild-to-moderate memory loss in the subjects of 55 years and older. Also, the frequency of side effects of saffron extract was similar to those of donepezil except for vomiting, which occurred more frequently in the donepezil group [98].

In another study, 46 patients with mild-to-moderate memory loss were treated with saffron for 16 weeks. The cognitive functions in the saffron-treated group were significantly better than placebo (ADAS-cog: F= 4·12, d.f.=1,p=0.04; CDR: F=4·12, d.f.=1, p=0·04) [99]. In another clinical trial investigating the effects of saffron supplementation 15 mg/twice a day on Alzheimer's disease patients, results showed that the administration of saffron significantly decreased levels of IL-1β and malondialdehyde (p=0.036 and p=0.021, respectively) while increasing total antioxidant capacity (TAC) (p=0.032) in serum samples of mild-to-moderate AD patients. Saffron showed improved inflammatory, antioxidant, and oxidative stress profiles, indicating saffron may have beneficial effects on circulatory markers in AD patients, highlighting its potential as a therapeutic intervention for this debilitating condition [62].

Six-week administration of saffron extract (30 mg/day) was effective in treating mild to moderate depression (F=0.13, d.f. = 1, p=0.71). These effects were like fluoxetine (F=0.13, d.f. = 1, p=0.71), [100], and imipramine 100 mg/day [101]. The efficacy of co-administration of hydroalcoholic extract of *C. sativus* (40 or 80 mg) and fluoxetine (30 mg/ day) was also investigated in a double-blind randomized clinical trial for six weeks. A dose of *C. sativus* 80 mg plus fluoxetine was more effective (p<0.05) than of *C. sativus* 40 mg and fluoxetine to treat mild to moderate depressive disorders [102]. In a randomized and double-blind clinical trial study, saffron supplementation of 30 mg/day statistically (p<0.05) improved the mood of subjects compared to the placebo group. At six weeks, *C. sativus* produced a significantly better outcome on the Hamilton depression rating scale than placebo (d.f. = 1, F=18.89, p<0.001) [103].

5.5. Foeniculum vulgare Mill. (Fennel)

F. vulgare (Apiaceae), a fennel from the Mediterranean region, has annual, biennial, or perennial variants. [104] *F. vulgare* is cultivated primarily for its aromatic fruits and essential oils, which contain high concentrations of trans-anethole (63.30 %), pinene (11.11 %), and fenchone (8.32 %) [105]. These metabolites exhibit anti-inflammatory, analgesic, and antioxidant properties [106]. Recent research suggests that oils effectively treat issues related to mental health disorders. *In vitro* studies have also revealed fennel's anti-stress and memory-enhancing capabilities. A double-blind, randomized study on 60 postmenopausal women found that fennel improved symptoms in those with pre-existing depression or anxiety [107].

In a research study conducted by Alvarado-García et al. in 2022 [108], the anxiolytic and antidepressant-like effects of the essential oils from *F. vulgare* aerial parts (EG1) and seeds (EG2) were evaluated. The anxiety and depression indexes were evaluated by Zung Self-Rating Anxiety Scale (SAS) and Zung Self-Rating Depression Scale (SDS). EG1 showed a small change in anxiety levels (d = 0.41; Δ= 0.40) and a slight decrease of 4.51 % in anxiety after the intervention. On the other hand, EG2 exhibited moderate changes in anxiety (d = 0.86; Δ = 0.85) and a significant decrease of 8.09 % in anxiety and 4.72 % in depression. These results suggest that the intervention had a positive impact on reducing anxiety and depression levels in both groups [108].

5.6. Matricaria chamomilla L. (Chamomile)

M. chamomilla (Asteraceae), or chamomile, is recognized for its potential in treating neurological conditions like GAD and comorbid depression [109]. A randomized, double-blind, placebo-controlled study showed a significant reduction in mean anxiety symptoms (p=0.047), and an exploratory study revealed significant decreases in total and core depression scores (p<0.05) [110]. The plant's efficacy is attributed to its complex phytochemical profile, terpenoids such as α-bisabolol and its oxides A and B, and phenolic metabolites like phenolic acids and

flavonoids. These metabolites have a synergistic effect, enhancing chamomile's clinical utility. Mao et al. [111] confirmed its sustained efficacy over 38 weeks. Additionally, chamomile improved sleep quality in the elderly, as measured by the Pittsburgh Sleep Quality Index (PSQI), and alleviated postpartum depression and sleeplessness [111]. In a study investigating the effects of *M. chamomilla* (1500 mg per day) on subjects with GAD and comorbid depression, it was found that there was a significant reduction in Hamilton Rating Scale for Depression (HRSD) core symptom scores ($p < 0.023$) and a trend towards reduction in HRSD total scores ($p = 0.14$) and Beck depression inventory (BDI) total scores ($p = 0.060$) in those with comorbid depression, indicating that the extract may have clinically meaningful antidepressant effects in addition to its anxiolytic activity [112].

Aromatherapeutic approaches using the essential oil are considered an alternative treatment for depression. Chamomile is an excellent reliever when patients with depression have physical and psychological discomfort. Chamomile tea made from chamomile flower heads can effectively relieve depressive symptoms and the sleep status of postpartum women, which provides a new idea to treat depression.

5.7. Melissa officinalis L. (Lemon balm)

M. officinalis (MO; Lamiaceae), also known as lemon balm, is native to the Mediterranean and Western Asia. It contains bioactive volatile compounds, triterpenes, and phenolic compounds [113].

Amongst the several botanicals that have been extensively studied for psychopharmacological effects, the leaf extract of *M. officinalis* has emerged as a promising agent for calming the central nervous system (CNS) and improving the low mood status. This property was comparatively evaluated *in vitro* by inhibition of GABA-T and Monoamine oxidase A (MAO-A) in hydrogen peroxide (H_2O_2)-exposed SH-SY5Y cells by innovative standardized phospholipid carrier-based (Phytosome™) MO extract (Relissa™) vs. an unformulated dry MO extract. Results indicated that Relissa™ demonstrated a strong GABA-T inhibitory effect with an IC_{50} value of 0.064 mg/mL, while the unformulated dry MO extract exhibited reduced potency (IC_{50} 0.27 mg/mL). Similarly, the Relissa™ MAO-A inhibitory effect was statistically improved even at low concentrations as compared to unformulated dry MO extract. Relissa™ demonstrated an improved neuroprotective antioxidant effect on SH-SY5Y cells against H2O2-induced oxidative stress. Compared to unformulated dry MO extract, Relissa™ exerted high protective effect on H_2O_2-exposed SH-SY5Y cells, leading to higher cells brain-derived neurotrophic factor (BDNF) expression levels. These results support the neuromodulating and neuroprotective properties of Relissa™, and its supplementation may help in the amelioration of emotional distress and related conditions [114].

In an *in vivo* study, the effectiveness of the MO extract was evaluated in combination with human umbilical cord blood stem cells (hUCBSCs) transplantation after contusive spinal cord injury (SCI) in Wistar rats. The results revealed that motor function (MO-hUCBSC: 15 ± 0.3, SCI: 8.2 ± 0.37, $p < 0.01$) sensory function (MOhUCBSC: 3.57 ± 0.19, SCI: 6.38 ± 0.23, $p < 0.01$) and Electromyography (EMG) recruitment index (MO-hUCBSC: 3.71 ± 0.18, SCI: 1.6 ± 0.1, $p < 0.01$) were significantly improved in the MO-hUCBSC group compared with SCI group, indicating its neuroprotective effects in SCI [115].

A double-blind study by Akhondzadeh et al., 2003 [116] evaluated the effect of MO extract using a fixed dose (60 drops/day) in patients with mild to moderate memory loss in patients aged between 65 and 80 years (n = 42; 18 women, 24 men). Results demonstrated significant cognitive improvements with statistically significant better outcomes on ADAS-cog and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scales (ADAS-cog: d.f. = 1, F = 6.93, $p = 0.01$; CDR: d.f. = 1, F=16.87, $p < 0.0001$). Agitation frequency also decreased, indicating that extract is of value in the management of mild to moderate memory loss and has a positive effect on agitation in such patients [116].

A 24-week trial tested MO extract richly containing rosmarinic acid

(RA: 500 mg) on patients with mild dementia associated with Alzheimer's disease with the aim to examine the safety and tolerability (primary endpoint) of RA (500 mg daily) and its clinical effects and disease-related biomarker changes (secondary endpoints). RA showed improved mean Neuropsychiatric Inventory Questionnaire (NPI-Q) in patients with memory loss, suggesting its role in mitigating neuropsychiatric symptoms. The effect of time × treatment interaction on NPI-Q scores was significant ($p < 0.05$). The mean NPI-Q scores improved by 0.5 points in the *M. officinalis* group and worsened by 0.7 points in the placebo group between baseline and the 24-week visit [66].

Further studies indicate its potential for mood improvement, with gains in depression anxiety stress scales (DASS) scores. A 600-mg dose of Melissa ameliorated the adverse mood effects of the defined intensity stressor simulation (DISS), with significantly ($p < 0.01$) increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing, with no reduction in inaccuracy, was observed after ingestion of the 300-mg dose [117,118] and in sleep quality in postmenopausal women. MO significantly improved the menopause-specific quality of life (MENQOL) domain scores compared with citalopram and placebo ($p < 0.001$). The mean ± standard deviation (SD) after eight weeks in the MO, citalopram, and placebo groups was 2.2 ± 0.84 versus 0.56 ± 0.58 versus 0.36 ± 0.55 in the vasomotor ($p < 0.001$), 1.02 ± 0.6 versus 0.28 ± 0.2 versus 0.17 ± 0.1 in the psychomotor-social ($p < 0.001$), 0.76 ± 0.4 versus 0.25 ± 0.1 versus 0.11 ± 0.1 in the physical and 2.3 ± 1.0 versus 0.35 ± 0.5 versus 0.41 ± 0.5 in the sexual domain, respectively [119].

5.8. Mentha × piperita L. (Peppermint)

M × piperita (MP), or peppermint (Lamiaceae), is a perennial flowering plant introduced to the Middle East and has diverse applications in the food, cosmetics, and medicine industries. Its essential oil is rich in menthol and menthone, which have anti-inflammatory, antispasmodic, antioxidant, and antibacterial properties [120,121].

In an *in vitro* study, the neuroprotective effect of ethanolic extract of MP (EthMP; 200 mg/kg) was assessed against rotenone-induced behavioural deficits, dopaminergic degeneration, oxidative stress and neuronal survival activity in mouse model of Parkinson's disease. Results showed that EthMP in mice treated with rotenone significantly ($p < 0.001$) prevented the rotenone-mediated motor dysfunctions compared to Parkinson's disease group (14.0 ± 1.2 m in MP+Rot vs control 30.8 ± 0.9 m) as assessed through open field, beam walk (reduction in time: 7.12 ± 0.75 s vs rotenone group 110.79 ± 4.5 s), pole climb down (reduction in time by 7.08 ± 0.45 s in MP+Rot vs 13.31 ± 0.86 s in Rot), stepping, tail suspension ($p < 0.001$), and stride length tests ($p < 0.001$). EthMP administration decreased the lipid peroxidation (from $49.4 \pm 3.7 \mu mol/g$ to $30.6 \pm 0.9 \mu mol/g$), increased glutathione (from $1.5 \pm 0.3 nmol/g$ to $3.5 \pm 0.14 nmol/g$) and increased SOD levels from $51.7 \pm 2.6 \mu mol/mg$ to $85.7 \pm 6.2 \mu mol/mg$, as well as glutathionetransferase ($p < 0.01$) and catalase ($p < 0.01$) activities in mouse brain. Moreover, EthMP extract prevented neurodegeneration in the mice (from 72.56 ± 3.4 % to 48.95 ± 2.08 %) and partially maintained dopamine levels. The expression of genes related to dopamine, antioxidant potential and synapses were modulated in MP extract treated mice brains. All these data indicates the potential of MP in clinical applications for management of symptoms associated with PD [60].

Peppermint has been shown to modulate neurotransmitter function, affecting 5-HT and dopamine levels and acting as a natural stress mitigator [122]. Its metabolites, including monoterpenes, have neurological effects such as cholinesterase inhibition and modulation of 5-HT3 and GABA receptors [123].

Stress, sleep disorders, and anxiety are common mental health problems affecting many university students. In a randomized controlled trial, the effect of oral MP (peppermint; 250 mg) was assessed on self-reported memory performance, anxiety, stress, and the quality of sleep in 124 science students at Taibah University. Results demonstrated

that at baseline, the mean scores in the anxiety scale were 42.3 for the students in the peppermint group and 41.5 for students in the control group. After four weeks, the mean score observed in the peppermint group was significantly reduced (p<0.05). In the Perceived Stress Scale (PSS), the results obtained as mean scores was 18.55 and 17.32 in the peppermint and control groups, respectively. After four weeks, the mean score observed was significantly decreased only in the peppermint group (p<0.05). Moreover, 74.19 % students were classified as poor sleepers at baseline, and this decreased to 35.48 % students after the peppermint treatment. These results indicated the efficacy of peppermint in reducing anxiety and stress, improving memory and sleep quality, and enhancing alertness and mood [124].

In a triple-blind randomized clinical trial, the hydroethanolic extract of MP showed the highest anti-depression effect in those patients who received 100 mg and 200 mg of the extract and the lowest rate allocated to the groups of 50 mg as compared to the placebo group (p=0.078), indicating its effectiveness in depressed patients [125].

In two clinical trials, it has been observed that peppermint essential oil inhalation significantly reduces anxiety in cardiac patients admitted to emergency department p≤0.05 [126,127].

5.9. Nigella sativa L. (Black cumin)

N. sativa (Ranunculaceae), also known as black cumin or black seed, has garnered scientific interest for its potential in managing issues related to mental health disorders. It has been employed in ancient medicinal systems like Unani and Ayurveda, rooted in the Arab, Asia, Africa, and Europe [128]. It is one of the most iconic medicinal plants of the MEA region. *N. sativa* essential oil (NSO) contains several bioactive metabolites like thymoquinone (TQ), thymohydroquinone, thymol, carvacrol, β-sitosterol and alkaloids like nigellicimine and nigellidine [129].

N. sativa has been linked to memory enhancement, potentially due to its antioxidant and anti-cholinesterase properties [64,130]. NSO improves open-field activity and elevated maze test performance *in vivo*, increasing 5-HT and tryptophan levels. TQ showed anti-anxiety effects by modulating γ-aminobutyric acid (GABA) and nitric oxide (NO) levels in the brain and plasma. TQ also shows significant anxiolytic effects under stress via reducing plasma nitrite and brain GABA concentration [131].

A randomized, double-blind, placebo-controlled trial by Mohan et al. (2023) [65], a thymoquinone-rich black cumin oil extract (BCO-5) significantly (p<0.05) modulated the stress-sleep-immunity axis with no side effects and restored restful sleep. 70 % of the participants in the BCO-5 group reported satisfaction with their sleep patterns on day 7 and 79 % on day 14. Additionally, both inter- and intra-group analyses of the total Pittsburgh Sleep Quality Index (PSQI) scores and component scores (sleep latency, duration, efficiency, quality, and daytime dysfunction) on days 45 and 90 showed the effectiveness of the BCO-5 in the improvement of sleep (p<0.05). Perceived Stress Scale (PSS-14) analysis revealed a significant reduction in stress upon both intra (p<0.001) and inter-group (p<0.001) comparisons. Also, there was a significant modulation in melatonin, cortisol, and orexin levels [65]. In a study by Sayeed MS et al., 2014 [132], healthy elderly volunteers took a 500-mg *N. sativa* capsule twice a day for nine weeks. At the end of that period, the authors observed improved cognition, memory, and attention through special tests [132]. Similarly, computed tomography scan performed on healthy adolescent males aged 14–17 years established the modulatory effects on cognition, mood, and anxiety of NS taken in the form of a 500-mg NS capsule once a day for four weeks [133].

The therapeutic effects of *N. sativa* extract on serum BDNF and depression score in patients with depression was assessed using the Depression, Anxiety, and Stress Scale-21 Items (DASS-21) questionnaire. The results showed a significantly decreased DASS-21 score in patients in the intervention group (50.1 ± 6.8) compared to placebo (58.2 ± 5.6, p<0.001). Furthermore, patients in the intervention group had

significantly decreased depression vs those in the placebo group (18.6 ± 2.7 vs. 23.4 ± 2.1 respectively). A significant increase in BDNF levels were observed in the intervention group after the treatments (29.4 ± 3.6 vs. 24.9 ± 2.1, p< 0.001). Serum BDNF levels had also significant reverse correlations with DASS-21 score (r=−0.35, p=0.011) and depression score (r = −0.45, p=0.001). These findings highlight the importance of exploring alternative treatments for depression such as herbs like *N. sativa* that target biological markers such as BDNF [71].

5.10. Rosmarinus officinalis L. (Rosemary)

The Mediterranean shrub *R. officinalis* (Lamiaceae) has garnered attention for its potential neurotherapeutic benefits. Carnosic acid and carnosol have shown effects in glycaemic management by reducing blood glucose levels *in vivo* and improving triglyceride profiles in Zucker rats [134,135]. Studies have also highlighted the neuroprotective properties of rosmarinic and ursolic acids, which enhanced spatial and recognition memory and reduced anxiety in A1–42-induced BALB/c mice [136].

It has been investigated for its role in central nervous system disorders, including memory loss diseases. Dietary inclusion of rosemary improved cognitive performance and mitigated age-related memory decline [134,135]. A randomized controlled trial indicated that rosemary extracts could improve human cognitive function and mood, possibly affecting cholinergic and GABAergic neurotransmission. Specifically, rosmarinic acid increased GABA levels in brain by inhibiting GABA transaminase (GABA-T) [137].

Rosemary (500 mg, twice daily, for a month) as a traditional herbal medicine might be used to enhance prospective and retrospective memory, reduce anxiety and depression, and promote sleep quality. The inhalation of rosemary oil in 144 healthy volunteers induced subjective effects on mood and objective effects on cognitive performance. Tukey post-hoc comparisons identified that the rosemary condition (mean = 200.03) produced significantly higher scores in secondary memory subfactor than the lavender condition (mean = 174.24) and the control condition (mean = 176.60), with p<0.05 in each case. Tukey post-hoc comparisons identified that the rosemary condition produced an increase in alertness (mean change = 5.51), compared to decreases for both the control condition (mean change = –3.06), p<0.05, and the lavender condition (mean change = 7.49), p<0.05) [138].

In another study, the essential oil of rosemary oil improved students' exam performance by enhancing free radical scavenging activity and decreasing cortisol levels. In a study by Pengelly et al., 2012 [26], rosemary powder (750 mg), the dose nearest to normal culinary consumption, showed positive influences on the speed of memory, the time taken to effectively regain information from both episodic and working memory, on 28 older adults (mean age, 75 years) which is a useful predictor of cognitive function during aging. At 750 mg, there was a significant improvement (p=0.01), and at 6000 mg, there was a significant impairment (p<0.01) compared with the placebo. These results point to the value of further studies on the effects of different doses of rosemary on memory and cognition over a longer period. "Continuity of attention" was significantly impaired at 1500 (p<0.001), 3000 (p=0.04), and 6000 mg (p<0.001) doses, and "quality of working memory" was significantly impaired at 750 (p=0.02), 1500 (p=0.01), and 6000 mg (p=0.01), in both cases compared with placebo [26].

5.11. Salvia officinalis L. (Garden Sage)

S. officinalis (Lamiaceae), commonly known as Garden Sage, is native to the Middle Eastern and Mediterranean regions. It contains various phytochemicals, including alkaloids, carbohydrates, fatty acids, glycosidic derivatives, phenolic compounds, polyacetylenes, and terpenes [139].

Recent research suggests its potential to mitigate cognitive decline by regulating the cholinergic system. *S. officinalis* purpurea essential oil

dose-dependently inhibits butyrylcholinesterase (BuChE) [140] and inhibits AChE in human post-mortem brain tissue and bovine erythrocytes [141,142].

Clinical evidence further supports its cognitive benefits. A randomized controlled trial (RCT) by Kennedy, Pace, et al. (2006) [141] found that a 300 mg/day dried leaf extract reduced anxiety in healthy young adults more effectively than a 600 mg/day dosage [141]. Both Sage treatments led to modulation of the stress-inducing effects of the Defined Intensity Stress Simulator (DISS) battery. This effect was most pronounced for the 300 mg dose, with both increased anxiety and decreased alertness during the battery at 1 h (anxiety (t(58)<3.9, p<0.001), alertness (t(58)<3.24, p<0.002) and 4 h (anxiety (t(58)<2.86, p<0.006), alertness (t(58)<2.7, p<0.009)) post-dose. The higher dose was associated with improved performance on the 'Stroop' module at both post-dose time points (1 h (t(58)=5.05, p<0.001), 4 h (t(58)=5.67, p<0.001)) [141].

A systematic review by Miroddi, Navarra et al., 2014 [143] corroborated its traditional use in enhancing memory and cognitive abilities [143]. Clinical trials confirm that *S. officinalis* enhances cognitive performance in healthy participants and patients with cognitive impairment or dementia. The essential oil of *S. officinalis* enhances prospective memory performance in healthy adults (Moss et al., 2010). *S. officinalis* extract produced a significantly better outcome on cognitive functions than placebo (ADAS-cog: F = 4.77, d.f. = 1, p<0.03) (CDR-SB: F = 10.84, d.f. =1, p<0.003). There were no significant differences in the two groups regarding observed side effects except agitation, which appears to be more frequent in the placebo group (p<0.09) [144]. Similarly, in another study, an ethanolic extract of *S. officinalis* improved memory and attention in healthy older subjects [145]. A randomized controlled trial by Akhondzadeh et al., 2003 [146] showed that a four-month treatment with hydroalcoholic extract of *S. officinalis* improved cognitive functions in patients with mild to moderate memory loss. At four months, *S. officinalis* extract produced a significantly better outcome on cognitive functions than placebo (ADAS-cog: F = 4.77, d.f. = 1, p=0.03) (CDR-SB: F = 10.84, d.f. = 1, p<0.003) [146]. *S. officinalis* shows promise as a therapeutic intervention for cognitive decline and related neurological issues, warranting further research.

5.12. *Sceletium tortuosum (L.) N.E.Br. (Kanna)*

S. tortuosum (a synonym of *Mesembryanthemum tortuosum* L.; Aizoaceae), commonly known as "kanna" or "kougoed," is a succulent medicinal plant native to the Cape provinces of South Africa [10]. It is traditionally consumed in various forms, including chewing, tea, tincture, and occasional smoking, to relieve abdominal pain and induce sleep in children [147]. It is used traditionally in South Africa for managing managing symptoms mimicking mental health disorders [67]. *S. tortuosum* contains alkaloids like mesembrine, mesembrenone, mesembrenol, tortuosamine, and channaine, influencing various central nervous system targets. Studies have demonstrated its inhibitory effects on 5-HT reuptake and phosphodiesterase-4 activity, making it commercially used to treat CNS-related disorders like stress, depression, and anxiety [10,148]. Moreover, it can potentially manage neurodegenerative and neurological conditions [10,149]. Its neuroprotective mechanisms include AChE inhibition, modulation of monoamine oxidases (MAOs), particularly MAO-B, relevant to PD's oxidative stress, and an impact on N-methyl-D-aspartate receptors (NMDAR), suggesting anti-depressant potential [150].

A pharmaco-functional magnetic resonance imaging (fMRI) investigation evaluated the effects of a single 25-mg dosage of Zembrin® (a 30 % water / 70 %ethanol V/V spray-dried extract) on anxiety-related amygdala activity and neurocircuitry in 16 healthy volunteers. The participants' brains were examined during perceptual load, emotion-matching, and frightened face exposure. After a single 25 mg dosage, Zembrin® lowered amygdala response to frightening faces (F (1,14)= 6.90, p=0.020, partial η2=0.33) under low perceptual load settings and dissociated amygdala–hypothalamus connection on the emotion-matching test. 25 mg daily Zembrin® improved cognitive flexibility and executive function. Subjects tolerated Zembrin® well and saw mood and sleep improvements [151].

In a follow-up study, 60 healthy male and female individuals (50–80 years old) were given 25 or 50 mg Zembrin® daily for six weeks to compare brain electrical activity to a placebo. Quantitative EEG showed that Zembrin® significantly (p<0.05) increased delta activity, theta, and alpha1 spectral power in the frontotemporal region, known for memory retrieval. Psychometric tests showed significant (p<0.05) improvement in arithmetic computation and number association from both doses. Zembrin® reduces anxiety, increases cognitive performance, and may improve mood in healthy people [152]. Likewise, Reay et al. (2020) investigated the anxiolytic properties of a single 25 mg dose of *S. tortuosum* standardized extract (Zembrin®) on induced anxiety/stress response in 20 healthy young volunteers. Zembrin® caused a reduction in subjective anxiety levels (F (1,18) = 0.105, p=0.750) and ameliorated subjective and physiological indicators of anxiety/stress in healthy volunteers [69]. Hoffman et al. (2020) [153] investigated the effects of eight days of 25 mg of *S. tortuosum* extracts supplementation in 60 recreationally trained college-aged (20–35 years) men and women. Compared with placebo (PL), *S. tortuosum* extract significantly improved complex reactive tasks that required subjects to respond to repeated visual stimuli with a cognitive load [153]. A significantly greater performance (p=0.05) was noted in the number of successful hits in mode B performance between ST and PL. The change in performance of ST (react to a visual performance while announcing a 5-digit number) (3.63±7.18 hits) was significantly greater than PL (0.23±12.42 hits). Moreover, a significant difference (p<0.001) was observed between ST and PL in reactive agility that required decision-making (e.g., direction of movement) [153].

5.13. *Valeriana officinalis L*

V. officinalis (Caprifoliaceae), native to Europe and western Asia and now grown in many regions, is recognized for its sedative effects, particularly in treating insomnia and anxiety and is a species of global importance for such treatments. Its active metabolites include sesquiterpenes, valeric acid, valepotriates, and amino acids like GABA [154]. Most likely, these act synergistically for clinical efficacy. Research indicates an effective insomnia dosage of between 300 and 600 mg. *In vivo*, rodent studies have validated its anxiolytic and anti-depressants effects, with valerenic acid as a potential key metabolite [155].

A randomized placebo-controlled study administering 81.3 mg of valepotriates daily for four weeks showed significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores. The valepotriate group presented a significant decrease in the total, somatic and psychic scores of HAM-A (T= 5.50, 3.50, and 5.00, respectively). The STAI-trait and state showed no significant differences (T= 25.00 and 25.50, respectively) [156]. Another study with a daily 600 mg valerian extract dose for one week reduced psychological and physiological stress reactivity, comparable to diazepam [70]. *V. officinalis* showed anti-obsessive and compulsive effects. In a randomized controlled trial, 31 adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for obsessive compulsive disorder (OCD) received aqueous extract (765 mg/day in a capsule) or placebo (30 mg/day talcum powder) for eight weeks. The results showed a significant difference in somnolence (p=0.02) [157]. Due to its sedative effects, caution must be exercised if other sedatives are administered and should not be used prior to driving or operating machinery [158].

5.14. *Vitis vinifera L. (Grape)*

V.vinifera (Vitaceae), native to the Eastern Mediterranean and Middle Eastern regions, including Iran and Turkey, is noted for its neuroprotective properties, primarily related to the outer layer of the berries

(grape skin). Its diverse bioactive metabolites include anthocyanin mono-glucosides in grape skins, with malvidin-3-O-glucoside being predominant [159]. Leaves contain tannins, flavonoids, and procyanidins, among other metabolites [160]. Fruits and seeds feature resveratrol, quercetin, and catechin, which have shown neuroprotective effects [161].

A study in Sprague-Dawley rats revealed *V. vinifera* dried fruit extract's impact on Amyloid Precursor Protein (APP) mRNA expression, indicating its anti-APP properties and effects in inhibiting DNA and RNA fragmentation [68]. It also exhibits antioxidant capacity, potentially affecting cholinergic receptors.

Clinical trials have shown its role in reducing amyloid plaques, Tau tangles, oxidative stress, and inflammation while enhancing cholinergic effects. A twelve-week administration of Cognigrape® herbal supplements was found safe and effective in enhancing cognitive profiles and promoting neuronal health. Mini-Mental State Examination (MMSE) scores were significantly improved after supplementation with Cognigrape® in comparison with baseline levels (p<0.0001) and placebo (r = 0.59, 0.95 % CI 0.11, 1.22; p<0.0001). Cognigrape® supplementation produced a significant reduction in Beck Depression Inventory (BDI) (-15.8 %) and Hamilton Anxiety Rating Scale (HARS) (-24.9 %) scores with respect to baseline levels (p<0.0001) and placebo (p<0.0001 for BDI and p<0.05 for HARS). Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score was significantly improved by Cognigrape® with respect to baseline levels and placebo (r = 0.55, 0.95 % CI 0.48, 6.07; p<0.0001). The comparison with the placebo revealed improvements in several parameters among participants receiving Cognigrape®: attention (p<0.001), language (p<0.05), immediate memory (p<0.0001), and delayed memory (p<0.0001) [162].

5.15. Withania somnifera (L.) Dunal (Ashwagandha)

W. somnifera (Solanaceae), commonly known as ashwagandha and widely used in Indian and Middle Eastern medical systems, has garnered attention for its potential in treating neurological disorders with reported anti-inflammatory, antioxidant, anti-cancer, anti-diabetic, and anti-asthmatic effects [163,164]. Traditionally used for various chronic conditions, including high blood pressure, depression, diabetes, arthritis, and in patients with memory loss, W. somnifera is also recognized for its stress-reduction, cognitive-enhancement, and immune-supporting properties [165–167]. Active metabolites like alkaloids, steroidal lactones (withanolides, withaferins), and steroidal saponins contribute to its therapeutic effects. W. somnifera can effectively suppress pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrating its anti-inflammatory capabilities [164]. Recent research has shown its potential to reduce type 2 inflammation markers, including TNF- α, IgE, and NF-β [168,169].

Based on a systematic review and meta-analysis, Ashwagandha extract had a small but significant positive impact on overall sleep quality [170]. Clinical studies by Auddy B. et al. 2008, Cooley K et al., 2009, and Chandrasekhar K et al., 2012 have collectively supported Ashwagandha's effectiveness in alleviating stress symptoms [171–174]. In a 60-day double-blind trial with 240 mg of ashwagandha extract (Shoden) administered daily, participants experienced reduced anxiety and stress, as measured by Hamilton Anxiety Rating Scale (HAM-A) and Depression, Anxiety and Stress Scale-21 (DASS-21) scales, along with lowered morning cortisol levels [25]. Further, in a double-blind placebo control study, the effect of W. somnifera extract was observed in patients with ICD-10 anxiety disorder for six weeks. Results demonstrated a trend for the anxiolytic superiority of *W. somnifera* over placebo at week two and a statistically significant (p<0.1) superiority at week six, indicating anxiolytic potential [175].

When compared to placebo, Ashwagandha-root extract (300 mg twice daily) was shown to be effective in enhancing both immediate and general memory in people with mild cognitive impairment (MCI) as evidenced by Wechsler Memory Scale III subtest scores for logical memory I (p=0.007), verbal paired associates I (p=0.042), faces I (p=0.020), family pictures I (p=0.006), logical memory II (p=0.006), verbal paired associates II (p=0.031), faces II (p=0.014), and family pictures II (p=0.006) [176]. Moreover, another randomized placebo-controlled study of a W. somnifera extract for the treatment of cognitive dysfunction in bipolar disorder showed significant improvement in cognitive performance, as evidenced by 3 cognitive tasks: digit span backward (p=0.035), Flanker neutral response time (p=0.033), and the social cognition response rating of Penn Emotional Acuity Test (p=0.045). A few modest adverse events occurred, and mood and anxiety scale scores remained stable [177].

6. Conclusions

Research on the effects of medicinal plants on the mind and body has a longstanding history in medicine and pharmacology. However, their application in treating mood disorders, insomnia, stress, anxiety, depression, and related conditions remains a largely unexplored area. Medicinal plants present a promising way of addressing issues related to mental health. The focus on the MEA and the medicinal plants of importance in this region points to the need for novel therapeutic and preventive approaches since these areas exhibit a significant burden of mental health conditions.

In this narrative review, scientific evidences cited under each medicinal plant include clinical, in vivo and in vitro studies. The clinical studies support; in vivo studies provide some limited evidence and the in vitro data or reported local/traditional use provide very limited evidence on the benefits of these medicinal plants in mental health related symptom management.

Despite the abundance of *in vitro* and *in vivo* investigations that support the pharmacological effects of different medicinal plant-based treatments, a notable disparity exists in applying these results in real-world medical settings. Also, there remains a gap in well-designed and reported clinical trials. Methodological constraints, including insufficient research design, limited sample sizes, and inappropriate endpoint selections, have impeded the advancement of these promising medicines from the laboratory to the clinic. Given the dynamic nature of the healthcare environment, it is crucial to use multifaceted strategies, particularly when addressing polygenic illnesses. Medicinal plant-based products, due to their composition of multiple constituents, present a feasible alternative to drugs that target a single mediator (e.g., an enzyme), thereby mitigating non-specific toxicity and inhibiting the development of drug resistance, most notably for minor self-limiting conditions. Subsequent investigations need to prioritize the implementation of rigorous clinical trials of chemically well-defined preparations to assess the safety and efficacy of these herbal therapies, thereby expediting their integration into conventional medical practice from their status as alternative treatments. Comprehending the underlying mechanisms of these botanical interventions is crucial for the progression of pharmaceutical interventions, particularly in mental health related issues. This will expand therapeutic options for various disorders and offer a more comprehensive and personalized approach to patient care.

CRediT authorship contribution statement

Michael Heinrich: Writing – review & editing, Supervision, Conceptualization. **Michael Goode:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization. **Morten Georg Jensen:** Writing – review & editing, Writing – original draft, Methodology, Data curation.

Declaration of Competing Interest

Morten Georg Jensen is employed by Haleon, a producer of herbal medicines and supplements. Michael Heinrich supported the project without funding but received funding in previous years for advice on developing herbal medical products from GSK Consumer Healthcare, later Haleon.

Data Availability

Data will be made available on request.

Acknowledgments

References

[1] W.M. Mcdonald, Overview of neurocognitive disorders, Focu-Am. Psychatr Publ. 15 (2017) 4–12, https://doi.org/10.1176/appi.focus.20160030.

[2] V.R. Muddapu, Sa.P. Dharshini, V.S. Chakravarthy, Neurodegenerative diseases - is metabolic deficiency the root cause? Front Neurosci. 14 (2020) 213, https://doi.org/10.3389/fnins.2020.00213.

[3] G. Park, H.S. Nhan, S.H. Tyan, Caspase activation and caspase-mediated cleavage of app is associated with Amyloid B-protein-induced synapse loss in Alzheimer's disease, Cell Rep. 31 (2020) 107839, https://doi.org/10.1016/j.celrep.2020.107839.

[4] S. Sirin, S. Nigdelioglu Dolanbay, B. Aslim, Role of plant derived alkaloids as antioxidant agents for neurodegenerative diseases, Health Sci. Rev. 6 (2023) 100071, https://doi.org/10.1016/j.hsr.2022.100071.

[5] M.F.P. Peres, J.P.P. Mercante, P.R. Tobo, Anxiety and depression symptoms and migraine: A symptom-based approach research, J. Headache Pain. 18 (2017) 37, https://doi.org/10.1186/s10194-017-0742-1.

[6] D. Arias, S. Saxena, S. Verguet, Quantifying the global burden of mental disorders and their economic value, EClinicalMedicine 54 (2022) 101675, https://doi.org/10.1016/j.eclinm.2022.101675.

[7] G. Castelpietra, A.K.S. Knudsen, E.E. Agardh, The burden of mental disorders, substance use disorders and self-harm among young people in Europe, 1990-2019: findings from the global burden of disease study 2019, Lancet Reg. Health Eur. 16 (2022) 100341, https://doi.org/10.1016/j.lanepe.2022.100341.

[8] H. Onohuean, A.O. Akiyode, O. Akiyode, Epidemiology of neurodegenerative diseases in the East African region: a meta-analysis, Front. Neurol. 13 (2022) 1024004, https://doi.org/10.3389/fneur.2022.1024004.

[9] D.F. Santomauro, A.M.M. Herrera, J. Shadid, Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the Covid-19 pandemic, Lancet 398 (2021) 1700–1712, https://doi.org/10.1016/s0140-6736(21)02143-7.

[10] M.C. Manganyi, C.C. Bezuidenhout, T. Regnier, A chewable cure "Kanna": biological and pharmaceutical properties of Sceletium Tortuosum, Molecules 26 (2021), https://doi.org/10.3390/molecules26092557.

[11] M. Kenda, N. Kočevar Glavač, M. Nagy, Medicinal plants used for anxiety, depression, or stress treatment: an update, Molecules 27 (2022), https://doi.org/10.3390/molecules27186021.

[12] X. Zhang H. World Health Organization, 2000, General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, World Health Organization.

[13] B. Jalil, A.Y. Naser, M.P. J, Herbal supplements in jordan: a cross-sectional survey of pharmacists' perspectives and knowledge, BMJ Open 12 (2022) e057405, https://doi.org/10.1136/bmjopen-2021-057405.

[14] H. Roberts, Accra. A Way Forward for Mental Health Care in Ghana? Lancet 357 (2001) 1859, https://doi.org/10.1016/s0140-6736(00)05020-0.

[15] M. Mander, L. Ntuli, N. Diederichs, Econ. Tradit. Med. Trade South Afr. Care Deliv. 2007 (2007) 189–196.

[16] E.A. Makundi, H.M. Malebo, P. Mhame, Role of traditional healers in the management of severe malaria among children below five years of age: the case of Kilosa and Handeni districts, Tanzania, Malar. J. 5 (2006) 58, https://doi.org/10.1186/1475-2875-5-58.

[17] A.A. Abdullahi, Trends and challenges of traditional medicine in Africa, Afr. J. Tradit. Complement Alter. Med 8 (2011) 115–123, https://doi.org/10.4314/ajtcm.v8i5.5.

[18] B. Saad, H. Azaizeh, O. Said, Tradition and perspectives of arab herbal medicine: a review, Evid. Based Complement Altern. Med. 2 (2005) 475–479, https://doi.org/10.1093/ecam/neh133.

[19] A. Abdolmaleki, M. Akram, M.M. Saeed, Herbal medicine as neuroprotective potential agent in human and animal models: a historical overview, J. Pharm. Care (2020) 75–82.

[20] M. Rashrash, J.C. Schommer, L.M. Brown, Prevalence and predictors of herbal medicine use among adults in the united states, J. Patient Exp. 4 (2017) 108–113.

[21] C. Calabrese, W.L. Gregory, M. Leo, Effects of a standardized Bacopa Monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial, J. Altern. Complement. Med. 14 (2008) 707–713.

[22] J.M. Gannon, J. Brar, A. Rai, Effects of a standardized extract of Withania somnifera (Ashwagandha) on depression and anxiety symptoms in persons with Schizophrenia participating in a randomized, placebo-controlled clinical trial, Ann. Clin. Psychiatry 31 (2019) 123–129.

[23] C. Kongkeaw, P. Dilokthornsakul, P. Thanarangsarit, Meta-analysis of randomized controlled trials on cognitive effects of Bacopa Monnieri extract, J. Ethnopharmacol. 151 (2014) 528–535.

[24] D. Langade, V. Thakare, S. Kanchi, Clinical evaluation of the pharmacological impact of Ashwagandha root extract on sleep in healthy volunteers and insomnia patients: a double-blind, randomized, parallel-group, placebo-controlled study, J. Ethnopharmacol. 264 (2021) 113276.

[25] A.L. Lopresti, S.J. Smith, H. Malvi, An investigation into the stress-relieving and pharmacological actions of an Ashwagandha (Withania somnifera) extract: a randomized, double-blind, placebo-controlled study, Medicine 98 (2019).

[26] A. Pengelly, J. Snow, S.Y. Mills, Short-term study on the effects of Rosemary on cognitive function in an elderly population, J. Med. Food 15 (2012) 10–17.

[27] S. Kumar, G.J. Dobos, T. Rampp, The significance of ayurvedic medicinal plants, J. Evid. Based Complement. Alter. Med 22 (2017) 494–501, https://doi.org/10.1177/2156587216671392.

[28] M. Braun, Neurol. Disord. Neuropsychol. Handb. (2008) 31.

[29] B.S. Mcewen, Physiology and neurobiology of stress and adaptation: central role of the brain, Physiol. Rev. 87 (2007) 873–904.

[30] M.S.J. Debora, V. Baba, S. Gomathi, Impact Stress Health, Narayana Nurs. J. 5 (2018) 11–14.

[31] D. Rai, G. Bhatia, T. Sen, Anti-stress effects of Ginkgo biloba and Panax ginseng: a comparative study, J. Pharmacol. Sci. 93 (2003) 458–464.

[32] H. Yaribeygi, Y. Panahi, H. Sahraei, The impact of stress on body function: a review, Excli J. 16 (2017) 1057.

[33] B. Brigitta, Pathophysiology of depression and mechanisms of treatment, Dialog. Clin. Neurosci. 4 (2002) 7–20.

[34] A. Garakani, J.W. Murrough, R.C. Freire, Pharmacotherapy of anxiety disorders: current and emerging treatment options, Front. Psychiatry 1412 (2020).

[35] X. Yang, Y. Fang, H. Chen, Global, regional and national burden of anxiety disorders from 1990 to 2019: results from the global burden of disease study 2019, Epidemiol. Psychiatr. Sci. 30 (2021) e36.

[36] M.G. Gottschalk, K. Domschke, Genetics of generalized anxiety disorder and related traits, Dialog. Clin. Neurosci. 19 (2017) 159–168, https://doi.org/10.31887/DCNS.2017.19.2/kdomschke.

[37] M.V. Mendlowicz, M.B. Stein, Quality of life in individuals with anxiety disorders, Am. J. Psychiatry 157 (2000) 669–682, https://doi.org/10.1176/appi.ajp.157.5.669.

[38] L. Wolgensinger, Cognitive behavioral group therapy for anxiety: recent developments, Dialog. Clin. Neurosci. 17 (2015) 347–351, https://doi.org/10.31887/DCNS.2015.17.3/lwolgensinger.

[39] N. Kugbey, T.A. Nortu, B. Akpalu, Prevalence of geriatric depression in a community sample in Ghana: analysis of associated risk and protective factors, Arch. Gerontol. Geriatr. 78 (2018) 171–176.

[40] M.P. Mattson, S. Maudsley, B. Martin, Bdnf and 5-Ht: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders, Trends Neurosci. 27 (2004) 589–594.

[41] G. Yadid, A. Friedman, Dynamics of the dopaminergic system as a key component to the understanding of depression, Prog. brain res. 172 (2008) 265–286.

[42] R. Mirchandaney, R. Barete, L.D. Asarnow, Moderators of cognitive behavioral treatment for insomnia on depression and anxiety outcomes, Curr. Psychiatry Rep. 24 (2022) 121–128.

[43] J.C. Levenson, D.B. Kay, D.J. Buysse, The pathophysiology of insomnia, Chest 147 (2015) 1179–1192.

[44] J.A. Dopheide, Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy, Am. J. Manag. Care 26 (2020) S76–S84.

[45] N. Nicolaides, A. Vgontzas I. Kritikou, 2000. Hpa Axis and Sleep.[Updated 2020 Nov 24], Endotext [Internet] Feingold KR, Anawalt B, Boyce A, et al, eds South Dartmouth (MA): MDText com, Inc.

[46] M.R. Zielinski, A.J. Gibbons, Neuroinflammation, sleep, and Circadian rhythms, Front. Cell. Infect. Microbiol. 12 (2022) 853096.

[47] M. Basta, G.P. Chrousos, A. Vela-Bueno, Chronic insomnia and the stress system, Sleep Med. Clin. 2 (2007) 279–291.

[48] T. Roth, T. Roehrs, R. Pies, Insomnia: PAthophysiology and Implications for Treatment, Sleep Med. Rev. 11 (2007) 71–79.

[49] L.L. Wellman, L. Yang, L.D.J.F.I.N. Sanford, Effects of Corticotropin Releasing Factor (Crf) on sleep and temperature following predictable controllable and uncontrollable stress in Mice, Front. Neurosci. 9 (2015) 258.

[50] R. Kölliker-Frers, L. Udovin, M. Otero-Losada, Neuroinflammation: an integrating overview of reactive-neuroimmune cell interactions in health and disease, Mediat. Inflamm. 2021 (2021) 1–20.

[51] D.M. Teleanu, A.-G. Niculescu, I.I. Lungu, An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases, Int. J. Mol. Sci. 23 (2022) 5938.

[52] K. Hatziagapiou, E. Kakouri, G.I. Lambrou, Antioxidant properties of Crocus sativus L. and its constituents and relevance to neurodegenerative diseases; focus

on Alzheimer's and Parkinson's disease, Curr. Neuropharmacol. 17 (2019) 377–402.

[53] K. Gopukumar, S. Thanawala, V. Somepalli, Efficacy and safety of Ashwagandha root extract on cognitive functions in healthy, stressed adults: a randomized, double-blind, placebo-controlled study, Evid. Based Complement Altern. Med. 2021 (2021) 8254344, https://doi.org/10.1155/2021/8254344.

[54] A. Panossian, G. Wikman, Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress—protective activity, Pharmaceuticals 3 (2010) 188–224.

[55] C. Abbo, S. Ekblad, P. Waako, The prevalence and severity of mental illnesses handled by traditional healers in two districts in Uganda, J. Afr. Health Sci. (2009) 9.

[56] D. Casteleijn, A. Steel, D. Bowman, A naturalistic study of herbal medicine for self-reported depression and/or anxiety a protocol, Integr. Med. Res. 8 (2019) 123–128, https://doi.org/10.1016/j.imr.2019.04.007.

[57] M.C. Ngoma, M. Prince, A. Mann, Common mental disorders among those attending primary health clinics and traditional healers in urban Tanzania, Br. J. Psychiatry 183 (2003) 349–355, https://doi.org/10.1192/bjp.183.4.349.

[58] S. Sahoo, S. Brijesh, Pharmacogenomic assessment of herbal drugs in affective disorders, Biomed. Pharmacother. 109 (2019) 1148–1162.

[59] H. Amu, E. Osei, P. Kofie, Prevalence and predictors of depression, anxiety, and stress among adults in Ghana: a community-based cross-sectional study, PloS One 16 (2021) e0258105.

[60] R. Anjum, C. Raza, M. Faheem, Neuroprotective potential of Mentha piperita extract prevents motor dysfunctions in mouse model of Parkinson's disease through anti-oxidant capacities, PLoS One 19 (2024) e0302102, https://doi.org/10.1371/journal.pone.0302102.

[61] M. Ghasemzadeh Rahbardar, H. Hosseinzadeh, Therapeutic Effects of Rosemary (Rosmarinus officinalis L.) and its active constituents on nervous system disorders, Iran. J. Basic Med. Sci. 23 (2020) 1100–1112, https://doi.org/10.22038/ijbms.2020.45269.10541.

[62] L.R. Marzabadi, S.M.B. Fazljou, M. Araj-Khodaei, Saffron reduces some inflammation and oxidative stress markers in Donepezil-treated mild-to-moderate Alzheimer's Disease patients: a randomized double-blind placebo-control trial 34 (2022) 100574.

[63] F.J. Mirza, S. Amber, D. Hassan, Rosmarinic acid and Ursolic acid alleviate deficits in cognition, synaptic regulation and adult hippocampal neurogenesis in an Aβ1-42-induced mouse model of Alzheimer's Disease, Phytomedicine 83 (2021) 153490.

[64] M.E. Mohan, J.V. Thomas, M.C. Mohan, A proprietary Black Cumin oil extract (Nigella sativa)(Blaqmax®) modulates stress-sleep-immunity axis safely: randomized double-blind placebo-controlled study, Front. Nutr. 10 (2023) 1152680.

[65] M.E. Mohan, J.V. Thomas, M.C. Mohan, A proprietary Black Cumin Oil Extract (Nigella sativa) (Blaqmax®)) modulates stress-sleep-immunity axis safely: randomized double-blind placebo-controlled study, Front. Nutr. 10 (2023) 1152680, https://doi.org/10.3389/fnut.2023.1152680.

[66] M. Noguchi-Shinohara, K. Ono, T. Hamaguchi, Safety and efficacy of Melissa officinalis extract containing Rosmarinic acid in the prevention of Alzheimer's disease progression, Sci. Rep. 10 (2020) 18627.

[67] T.L. Olatunji, F. Siebert, A.E. Adetunji, Sceletium Tortuosum: a review on its phytochemistry, pharmacokinetics, biological, pre-clinical and clinical activities, J. Ethnopharmacol. 287 (2022) 114711, https://doi.org/10.1016/j.jep.2021.114711.

[68] D. Rapaka, V.R. Bitra, T.C. Vishala, Vitis vinifera acts as Anti-Alzheimer's agent by modulating biochemical parameters implicated in cognition and memory, J. Ayurveda Integr. Med. 10 (2019) 241–247.

[69] J. Reay, M.A. Wetherell, E. Morton, Sceletium Tortuosum (Zembrin®) ameliorates experimentally induced anxiety in healthy volunteers, Hum. Psychopharmacol. Clin. Exp. 35 (2020) 1–7.

[70] N. Shinjyo, G. Waddell, J. Green, Valerian root in treating sleep problems and associated disorders—a systematic review and meta-analysis, J. Evid. Based Integr. Med. 25 (2020) 2515690X20967323.

[71] A.R. Zadeh, A.F. Eghbal, S.M. Mirghazanfari, 2022. Nigella Sativa Extract in the Treatment of Depression and Serum Brain-derived Neurotrophic Factor (Bdnf) Levels, 27, 28.

[72] J. Gregory, Y.V. Vengalasetti, D.E. Bredesen, Neuroprotective herbs for the management of Alzheimer's disease, Biomolecules 11 (2021) 543.

[73] S. Aguiar, T. Borowski, Neuropharmacological review of the nootropic herb Bacopa monnieri, Rejuvenation Res. 16 (2013) 313–326.

[74] A.S. Abdul Manap, S. Vijayabalan, P. Madhavan, Bacopa monnieri, a neuroprotective lead in Alzheimer Disease: a review on its properties, mechanisms of action, and preclinical and clinical studies, Drug Target Insights 13 (2019) 1177392819866412, https://doi.org/10.1177/1177392819866412.

[75] N. Uabundit, J. Wattanathorn, S. Mucimapura, Cognitive enhancement and neuroprotective effects of Bacopa monnieri in Alzheimer's disease model, J. Ethnopharmacol. 127 (2010) 26–31, https://doi.org/10.1016/j.jep.2009.09.056.

[76] J.M. Brimson, M.I. Prasanth, W. Plaingam, Bacopa monnieri (L.) Wettst. Extract protects against glutamate toxicity and increases the longevity of Caenorhabditis elegans, J. Tradit. Complement. Med. 10 (2020) 460–470.

[77] R. Khan, A. Krishnakumar, C. Paulose, Decreased glutamate receptor binding and Nmda R1 gene expression in hippocampus of pilocarpine-induced epileptic rats: neuroprotective role of Bacopa monnieri extract, Epilepsy Behav. 12 (2008) 54–60.

[78] S. Goswami, A. Saoji, N. Kumar, Effect of Bacopa monnieri on cognitive functions in Alzheimer's disease patients, Int. J. Collab. Res. Int. Med. Public Health 3 (2011) 285–293.

[79] S. Benson, L.A. Downey, C. Stough, An acute, double-blind, placebo-controlled cross-over study of 320 Mg and 640 Mg doses of Bacopa monnieri (Cdri 08) on multitasking stress reactivity and mood, Phytother. Res. 28 (2014) 551–559.

[80] S. Roodenrys, D. Booth, S. Bulzomi, Chronic effects of Brahmi (Bacopa monnieri) on human memory, Neuropsychopharmacology 27 (2002) 279–281.

[81] M.P. Pase, J. Kean, J. Sarris, The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials, J. Altern. Complement. Med. 18 (2012) 647–652.

[82] S.F. Nabavi, F. Maggi, M. Daglia, Pharmacological effects of Capparis spinosa L, Phytother. Res. 30 (2016) 1733–1744.

[83] D. Rivera, C. Inocencio, C. Obón, Review of food and medicinal uses of capparis L. Subgenuscapparis (Capparidaceae), Econ. Bot. 57 (2003) 515–534.

[84] H. Annaz, Y. Sane, G.T.M. Bitchagno, Caper (Capparis spinosa L.): an updated review on its phytochemistry, nutritional value, traditional uses, and therapeutic potential, Front. Pharmacol. 13 (2022) 878749.

[85] A. Goel, A. Garg, A. Kumar, Effect of Capparis spinosa Linn. Extract on Lipopolysaccharide-induced cognitive impairment in rats, Indian J. Exp. Biol. 54 (2016) 126–132.

[86] N.H. Turgut, H. Kara, E. Arslanbaş, Effect of Capparis spinosa L. On cognitive impairment induced by D-Galactose in mice Via inhibition of oxidative stress, Turk. J. Med. Sci. 45 (2015) 1127–1136, https://doi.org/10.3906/sag-1405-95.

[87] N. Mohebali, S.A. Shahzadeh Fazeli, H. Ghafoori, Effect of flavonoids rich extract of capparis spinosa on inflammatory involved genes in amyloid-beta peptide injected rat model of Alzheimer's Disease, Nutr. Neurosci. 21 (2018) 143–150.

[88] N. Mirzakhani, A.A. Farshid, E. Tamaddonfard, Comparison of the effects of hydroalcoholic extract of Capparis spinosa fruit, quercetin and vitamin E on Monosodium Glutamate-induced toxicity in rats, Vet. Res. Forum 11 (2020) 127–134, https://doi.org/10.30466/vrf.2018.83041.2091.

[89] K.J. Gohil, J.A. Patel, A.K. Gajjar, Pharmacological review on Centella asiatica: a potential herbal cure-all, Indian J. Pharm. Sci. 72 (2010) 546.

[90] A.A. Farooqui, T. Farooqui, A. Madan, Ayurvedic medicine for the treatment of dementia: mechanistic aspects, Evid. Based Complement. Med. 2018 (2018).

[91] J. Bradwejn, Y. Zhou, D. Koszycki, A double-blind, placebo-controlled study on the effects of Gotu Kola (Centella asiatica) on acoustic startle response in healthy subjects, J. Clin. Psychopharmacol. 20 (2000) 680–684.

[92] U. Jana, T. Sur, L. Maity, A Clinical Study on the Management of Generalized Anxiety Disorder with Centella asiatica, Nepal Med. Coll. J. 12 (2010) 8–11.

[93] P. Puttarak, P. Dilokthornsakul, S. Saokaew, Effects of Centella asiatica (L.) Urb. on cognitive function and mood related outcomes: a systematic review and meta-analysis, Sci. Rep. 7 (2017) 10646.

[94] K.M. Farhana, R.G. Malueka, S. Wibowo, Effectiveness of Gotu Kola extract 750 Mg and 1000 Mg compared with folic acid 3 Mg in improving vascular cognitive impairment after stroke, Evid. Based Complement. Altern. Med. 2016 (2016).

[95] A.L. Lopresti, P.D. Drummond, Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action, Hum. Psychopharmacol. 29 (2014) 517–527, https://doi.org/10.1002/hup.2434.

[96] M.P. Munirah, M.N. Norhayati, M. Noraini, Crocus sativus for insomnia: a systematic review and meta-analysis, Int. J. Environ. Res. Public Health 19 (2022) 11658.

[97] A. Akhondzadeh Basti, E. Moshiri, A.A. Noorbala, Comparison of petal of Crocus sativus L. And Fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized, Prog. Neuropsychopharmacol. Biol. Psychiatry 31 (2007) 439–442, https://doi.org/10.1016/j.pnpbp.2006.11.010.

[98] S. Akhondzadeh, M. Shafiee Sabet, M.H. Harirchian, A 22-week, multicenter, randomized, double-blind controlled trial of crocus sativus in the treatment of mild-to-moderate Alzheimer's disease, Psychopharmacology 207 (2010) 637–643.

[99] S. Akhondzadeh, M.S. Sabet, M. Harirchian, Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial, J. Clin. Pharm. Ther. 35 (2010) 581–588.

[100] A. Noorbala, S. Akhondzadeh, N. Tahmacebi-Pour, Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial, J. Ethnopharmacol. 97 (2005) 281–284.

[101] S. Akhondzadeh, H. Fallah-Pour, K. Afkham, Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [Isrctn45683816], BMC Complement. Altern. Med. 4 (2004) 1–5.

[102] S.M. Moosavi, M. Ahmadi, M. Amini, The effects of 40 and 80 Mg hydro-alcoholic extract of Crocus sativus in the treatment of mild to moderate depression, J. Mazandaran Univ. Med. Sci. 24 (2014) 48–53.

[103] S. Akhondzadeh, N. Tahmacebi-Pour, A.A. Noorbala, Crocus sativus L. In the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial, Phytother. Res. 19 (2005) 148–151.

[104] N. Jadid, A.F. Widodo, D. Ermavitalini, The medicinal Umbelliferae plant fennel (Foeniculum vulgare Mill.): cultivation, traditional uses, phytopharmacological properties, and application in animal husbandry, Arab. J. Chem. (2023) 104541.

[105] M. Korinek, H. Handoussa, Y.-H. Tsai, 2021. Anti-Inflammatory and Antimicrobial Volatile Oils: Fennel and Cumin Inhibit Neutrophilic Inflammation Via Regulating Calcium and Mapks, 12, 674095.

[106] S. Koppula, H. Kumar, Foeniculum vulgare Mill (Umbelliferae) attenuates stress and improves memory in wister rats, Trop. J. Pharm. Res. 12 (2013) 553–558.

[107] M. Ghazanfarpour, F. Mohammadzadeh, P. Shokrollahi, Effect of Foeniculum vulgare (Fennel) on symptoms of depression and anxiety in postmenopausal women: a double-blind randomised controlled trial, J. Obstet. Gynaecol. 38 (2018) 121–126.

[108] Pa.A. Alvarado-García, M.R. Soto-Vasquez, L.E. Rosales-Cerquin, 2022. Anxiolytic and Antidepressant-like Effects of Foeniculum Vulgare Essential Oil, 14.

[109] A. El Mihyaoui, J.C. Esteves Da Silva, S. Charfi, Chamomile (Matricaria chamomilla L.): a review of ethnomedicinal use, phytochemistry and pharmacological uses, Life 12 (2022) 479.

[110] J.D. Amsterdam, Y. Li, I. Soeller, A randomized, double-blind, placebo-controlled trial of Oral Matricaria Recutita (Chamomile) extract therapy of generalized anxiety disorder, J. Clin. Psychopharmacol. 29 (2009) 378.

[111] S. Miraj, S. Alesaeidi, A systematic review study of therapeutic effects of Matricaria Recuitta Chamomile (Chamomile), Electron. Physician 8 (2016) 3024.

[112] J.D. Amsterdam, Q.S. Li, S.X. Xie, Putative antidepressant effect of Chamomile (Matricaria chamomilla L.) oral extract in subjects with comorbid generalized anxiety disorder and depression, J. Alter. Complement Med. 26 (2020) 813–819, https://doi.org/10.1089/acm.2019.0252.

[113] A. Shakeri, A. Sahebkar, B. Javadi, Melissa officinalis L.–a review of its traditional uses, phytochemistry and pharmacology, J. Ethnopharmacol. 188 (2016) 204–228.

[114] M. Kara, S. Sahin, F. Rabbani, An in vitro analysis of an innovative standardized phospholipid carrier-based melissa officinalis L. Extract as a potential neuromodulator for emotional distress and related conditions, Front. Mol. Biosci. 11 (2024) 1359177, https://doi.org/10.3389/fmolb.2024.1359177.

[115] S.R. Hosseini, G. Kaka, M.T. Joghataei, Assessment of neuroprotective properties of Melissa officinalis in combination with human umbilical cord blood stem cells after spinal cord injury 8 (2016) 1759091416674833.

[116] S. Akhondzadeh, M. Noroozian, M. Mohammadi, Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial, J. Neurol., Neurosurg., Psychiatry 74 (2003) 863.

[117] D.O. Kennedy, W. Little, A.B. Scholey, Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm), Psychosom. Med. 66 (2004) 607–613.

[118] A. Scholey, A. Gibbs, C. Neale, Anti-stress effects of lemon balm-containing foods, Nutrients 6 (2014) 4805–4821.

[119] M. Shirazi, M.N. Jalalian, M. Abed, The effectiveness of Melissa officinalis L. Versus citalopram on quality of life of menopausal women with sleep disorder: a randomized double-blind clinical trial, Rev. Bras. De. Ginecol. e Obstetrícia 43 (2021) 126–130.

[120] M.S. Baliga, S. Rao, Radioprotective potential of mint: a brief review, J. Cancer Res. Ther. 6 (2010) 255–262.

[121] D.L. Mckay, J.B. Blumberg, A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.), Phytother. Res. Int. J. Devoted Pharmacol. Toxicol. Eval. Nat. Prod. Deriv. 20 (2006) 619–633.

[122] T. Parveen, N. Amin, D. Saleem, Antistress effect of Mentha piperita in rats and the role of brain serotonin and dopamine, Asian J. Pharm. Biol. Res. (2012) 2.

[123] D. Kennedy, E. Okello, P. Chazot, Volatile Terpenes and brain function: investigation of the cognitive and mood effects of Mentha× Piperita L. essential oil with in vitro properties relevant to central nervous system function, Nutrients 10 (2018) 1029.

[124] A.A. R, The Effect of Mentha piperita L. On the Mental Health Issues of University Students: A Pilot Study, J. Pharm. Pharmacogn. Res 9 (2021) 49–57.

[125] S. Najafi Doulatabad, N. Hashemi, Z. Mohebi Nobandegani, The effect of hydroalcoholic extract of Mentha piperita (Complement Treatment) on severity of depressed patients, Armaghane danesh 14 (2009) 83–90.

[126] A. Lotfi, H. Shiri, R. Ilkhani,. The Efficacy of Aromatherapy with Melissa officinalis in Reducing Anxiety in Cardiac Patients: A Randomized Clinical Trial. 2019.

[127] M. Soleimani, L.S. Kashfi, M. Mirmohamadkhani, The effect of aromatherapy with peppermint essential oil on anxiety of cardiac patients in emergency department: a placebo-controlled study, Complement Ther. Clin. Pr. 46 (2022) 101533, https://doi.org/10.1016/j.ctcp.2022.101533.

[128] M.A. Hannan, M.A. Rahman, Aa.M. Sohag, Black Cumin (Nigella sativa L.): a comprehensive review on phytochemistry, health benefits, molecular pharmacology, and safety, Nutrients 13 (2021) 1784.

[129] S. Samarghandian, T. Farkhondeh, F. Samini, A review on possible therapeutic effect of Nigella sativa and Thymoquinone in neurodegenerative diseases, CNS Neurol. Disord. Drug Targets 17 (2018) 412–420.

[130] F. Beheshti, M. Khazaei, M. Hosseini, Neuropharmacological effects of Nigella sativa, Avicenna J. Phytomed. 6 (2016) 104–116.

[131] S. Samarghandian, T. Farkhondeh, F. Samini, A review on possible therapeutic effect of Nigella sativa and Thymoquinone in neurodegenerative diseases, CNS Neurol. Disord. Drug Targets 17 (2018) 412–420, https://doi.org/10.2174/1871527317666180702101455.

[132] M.S.B. Sayeed, T. Shams, S.F. Hossain, Nigella sativa L. seeds modulate mood, anxiety and cognition in healthy adolescent males, J. Ethnopharmacol. 152 (2014) 156–162.

[133] M.S. Bin Sayeed, T. Shams, S. Fahim Hossain, Nigella sativa L. Seeds modulate mood, anxiety and cognition in healthy adolescent males, J. Ethnopharmacol. 152 (2014) 156–162, https://doi.org/10.1016/j.jep.2013.12.050.

[134] J.M. Andrade, C. Faustino, C. Garcia, Rosmarinus officinalis L.: an update review of its phytochemistry and biological activity, Future Sci. OA 4 (2018) FSO283.

[135] M.R. Kamli, Aa.M. Sharaf, J.S. Sabir, Phytochemical screening of Rosmarinus officinalis L. As a potential anticholinesterase and antioxidant–medicinal plant for cognitive decline disorders, Plants 11 (2022) 514.

[136] F.J. Mirza, S. Amber, Sumera, Rosmarinic acid and ursolic acid alleviate deficits in cognition, synaptic regulation and adult Hippocampal neurogenesis in an Aβ(1-42)-induced mouse model of Alzheimer's disease, Phytomedicine 83 (2021) 153490, https://doi.org/10.1016/j.phymed.2021.153490.

[137] C. Ulbricht, T.R. Abrams, A. Brigham, An evidence-based systematic review of Rosemary (Rosmarinus officinalis) by the Natural Standard Research Collaboration, J. Diet. Suppl. 7 (2010) 351–413.

[138] M. Moss, J. Cook, K. Wesnes, Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults, Int. J. Neurosci. 113 (2003) 15–38.

[139] A. Ghorbani, M. Esmaeilizadeh, Pharmacological properties of Salvia officinalis and its components, J. Tradit. Complement. Med. 7 (2017) 433–440.

[140] S.U. Savelev, E.J. Okello, E.K. Perry, Butyryl-and Acetyl-cholinesterase inhibitory activities in essential oils of Salvia species and their constituents, Phytother. Res. Int. J. Devoted Pharmacol. Toxicol. Eval. Nat. Prod. Deriv. 18 (2004) 315–324.

[141] D.O. Kennedy, S. Pace, C. Haskell, Effects of Cholinesterase Inhibiting Sage (Salvia officinalis) on mood, anxiety and performance on a psychological stressor battery, Neuropsychopharmacology 31 (2006) 845–852.

[142] N.S. Perry, P.J. Houghton, P. Jenner, Salvia Lavandulaefolia essential oil inhibits cholinesterase in vivo, Phytomedicine 9 (2002) 48–51.

[143] M. Miroddi, M. Navarra, M.C. Quattropani, Systematic review of clinical trials assessing pharmacological properties of S Alvia species on memory, cognitive impairment and A Lzheimer's disease, CNS Neurosci. Ther. 20 (2014) 485–495.

[144] L. Moss, M. Rouse, K.A. Wesnes, Differential effects of the aromas of salvia species on memory and mood, Hum. Psychopharmacol. Clin. Exp. 25 (2010) 388–396.

[145] A.B. Scholey, N.T. Tildesley, C.G. Ballard, An extract of Salvia (Sage) with anticholinesterase properties improves memory and attention in healthy older volunteers, Psychopharmacology 198 (2008) 127–139.

[146] S. Akhondzadeh, M. Noroozian, M. Mohammadi, Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial, J. Clin. Pharm. Ther. 28 (2003) 53–59.

[147] N. Gericke, A. Viljoen, Sceletium—a review update, J. Ethnopharmacol. 119 (2008) 653–663.

[148] J.M. Carpenter, M.K. Jourdan, E.M. Fountain, The Effects of Sceletium Tortuosum (L.) Ne Br. extract fraction in the chick anxiety-depression model, J. Ethnopharmacol. 193 (2016) 329–332.

[149] B.-E. Van Wyk, N. Gericke, People's Plants: A Guide to Useful Plants of Southern Africa, Briza publications, 2000.

[150] Y. Luo, L. Shan, L. Xu, A network pharmacology-based approach to explore the therapeutic potential of Sceletium Tortuosum in the treatment of neurodegenerative disorders, Plos One 17 (2022) e0273583.

[151] D. Terburg, S. Syal, L.A. Rosenberger, Acute effects of Sceletium Tortuosum (Zembrin), a dual 5-Ht reuptake and Pde4 inhibitor, in the human amygdala and its connection to the hypothalamus, Neuropsychopharmacology 38 (2013) 2708–2716, https://doi.org/10.1038/npp.2013.183.

[152] W. Dimpfel, N. Gericke, S. Suliman, Effect of Zembrin® on brain electrical activity in 60 older subjects after 6 Weeks of daily intake. A prospective, randomized, double-blind, placebo-controlled, 3-armed study in a parallel design, World J. Neurosci. 7 (2016) 140–171.

[153] J.R. Hoffman, I. Markus, G. Dubnov-Raz, Ergogenic effects of 8 Days of Sceletium Tortuosum supplementation on mood, visual tracking, and reaction in recreationally trained men and women, J. Strength Cond. Res. 34 (2020) 2476–2481.

[154] S. Hadley, J.J. Petry, Valerian, Am. Fam. Physician 67 (2003) 1755–1758.

[155] M. Hattesohl, B. Feistel, H. Sievers, Extracts of valeriana officinalis L. Sl show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties, Phytomedicine 15 (2008) 2–15.

[156] R. Andreatini, V.A. Sartori, M.L. Seabra, Effect of valepotriates (Valerian Extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study, Phytother. Res. Int. J. Devoted Pharmacol. Toxicol. Eval. Nat. Prod. Deriv. 16 (2002) 650–654.

[157] S. Pakseresht, H. Boostani, M. Sayyah, Extract of Valerian Root (Valeriana officinalis L.) Vs. placebo in treatment of obsessive-compulsive disorder: a randomized double-blind study, J. Complement. Integr. Med. 8 (2011).

[158] E.J. Edwards, M.S. Edwards M.J.E. Lyvers, 2015. Cognitive Trait Anxiety, Situational Stress, and Mental Effort Predict Shifting Efficiency: Implications for Attentional Control Theory, 15, 350.

[159] A.A. Watrelot, E.L. Norton, Chemistry and reactivity of Tannins in Vitis Spp.: a review, Molecules 25 (2020) 2110.

[160] L. Micheli, L. Mattoli, A. Maidecchi, Effect of Vitis vinifera hydroalcoholic extract against oxaliplatin neurotoxicity: in vitro and in vivo evidence, Sci. Rep. 8 (2018) 14364.

[161] M. Nassiri-Asl, H. Hosseinzadeh, Review of the pharmacological effects of Vitis vinifera (Grape) and its bioactive constituents: an update, Phytother. Res. 30 (2016) 1392–1403.

[162] G. Calapai, F. Bonina, A. Bonina, A randomized, double-blinded, clinical trial on effects of a Vitis vinifera extract on cognitive function in healthy older adults, J. Front. Pharmacol. 8 (2017) 776.

[163] R. Agarwal, S. Diwanay, P. Patki, Studies on immunomodulatory activity of Withania somnifera (Ashwagandha) extracts in experimental immune inflammation, J. Ethnopharmacol. 67 (1999) 27–35.

[164] S. Khan, F. Malik, K.A. Suri, Molecular Insight into the Immune up-regulatory properties of the leaf extract of Ashwagandha and identification of Th1 immunostimulatory chemical entity, Vaccine 27 (2009) 6080–6087.

[165] S. Kulkarni, A. Dhir, Withania somnifera: an Indian Ginseng, Prog. Neuro-psychopharmacol. Biol. Psychiatry 32 (2008) 1093–1105.

[166] M. Rasool, P. Varalakshmi, Immunomodulatory ROle of Withania somnifera root powder on experimental induced inflammation: an in vivo and in vitro study, Vasc. Pharmacol. 44 (2006) 406–410.

[167] N. Singh, M. Bhalla, P. De Jager, An overview on Ashwagandha: A Rasayana (Rejuvenator) of ayurveda, Afr. J. Tradit. Complement. Altern. Med. 8 (2011).

[168] H.H. Alanazi, E. Elfaki, The immunomodulatory role of Withania somnifera (L.) Dunal in inflammatory diseases, Front. Pharmacol. 14 (2023) 430.

[169] H. Ichikawa, Y. Takada, S. Shishodia, Withanolides potentiate apoptosis, inhibit invasion, and abolish Osteoclastogenesis through Suppression of Nuclear Factor-Kb (Nf-Kb) activation and Nf-Kb–regulated gene expression, Mol. Cancer Ther. 5 (2006) 1434–1445.

[170] K.L. Cheah, M.N. Norhayati, L. Husniati Yaacob, Effect of Ashwagandha (Withania somnifera) extract on sleep: a systematic review and meta-analysis, PloS One 16 (2021) e0257843.

[171] B. Abedon, B. Auddy, J. Hazra, A Standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo-controlled study, Jana 11 (2008) 50–56.

[172] K. Chandrasekhar, J. Kapoor, S. Anishetty, A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults, Indian J. Psychol. Med. 34 (2012) 255–262.

[173] K. Cooley, O. Szczurko, D. Perri, Naturopathic care for anxiety: a randomized controlled trial Isrctn78958974, PLoS One 4 (2009) e6628.

[174] S. Zahiruddin, P. Basist, A. Parveen, Ashwagandha in brain disorders: a review of recent developments, J. Ethnopharmacol. 257 (2020) 112876.

[175] C. Andrade, A. Aswath, S. Chaturvedi, A double-blind, placebo-controlled evaluation of the anxiolytic efficacy of an ethanolic extract of Withania somnifera, Indian J. Psychiatry 42 (2000) 295.

[176] D. Choudhary, S. Bhattacharyya, S. Bose, Efficacy and safety of Ashwagandha (Withania somnifera (L.) Dunal) root extract in improving memory and cognitive functions, J. Diet. Suppl. 14 (2017) 599–612.

[177] K.N. Chengappa, C.R. Bowie, P.J. Schlicht, Randomized placebo-controlled adjunctive study of an extract of Withania somnifera for cognitive dysfunction in bipolar disorder, J. Clin. Psychiatry 74 (2013) 1076–1083. ⟨https://doi.org/10.4088/JCP.13m08413s⟩.