Depression and Treatment with Effective Herbs

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Abstract

Depression is a common psychiatric disease and one of the main causes of disability worldwide. In spite of certain developments in this field, chemical and synthetic drugs used for the treatment of depression may disrupt the treatment process due to numerous side effects and high cost. Today, the goal of using a potential method for treating depression involves the use of medicinal and phytochemical plants, which have many therapeutic benefits. Studies have shown that medicinal plants affect the nervous system and exert antidepressant effects in various ways, including synaptic regulation of serotonin, noradrenaline and dopamine, and inflammatory mediators. In this study, depression as well as the factors and mechanisms involved in its development are first addressed, and then medicinal plants effective in the treatment of depression along with their mechanisms of actions are reported

Keywords: Depression, biomarkers, bio-factors, mechanism, medicinal plants.

1. INTRODUCTION

Depression is one of the five most commonly diagnosed diseases across the world and is expected to be the second leading cause of disability worldwide by 2020 [1]. The global prevalence of major depression is 4.7%. This means that out of every 20 people, one individual is affected by depression. The prevalence of depression in the elderly people and in women is higher than other populations [2]. The depression prevalence in women is 10-25% and in men is 5-12% [3], i.e., the prevalence of depression in women is about twice that of men. According to the definition of the American Psychiatric Association, depression is a heterogeneous disorder that is often associated with physiological, behavioral and psychological symptoms [4]. Depression causes mood changes, difficulty in thinking, and loss of interest as well as physical problems such as headache, sleep disorders, loss of energy and sexual problems [5, 6]. The causes of the disease include genetic factors, chemical changes in the brain, psychosocial issues, psychodynamic factors, changes in hormonal levels, various physical illnesses, medications and malnutrition, and even diet. Recently, internal stressors such as changes in the serum levels of cholesterol, triglycerides, glucose, and coagulation factors have been reported to be associated with depression [7]. Dysfunction of brain monoamine receptors, monoamine secretion, general dysfunction of the monoamine system and dysfunction of the second messenger system are the main focus of pathophysiological hypotheses regarding depression [8, 9, 10]. A number of drugs are available for the treatment of depression, but clinical evaluation of these drugs has shown recurrence of the disease and certain side effects in addition to drug interactions. Tricyclic antidepressants can cause certain complications, including dry mouth, distress, constipation, dizziness, thirst, blurred vision, high blood pressure, inability to drive, and sexual dysfunction [5, 11, 12]. Monoamine oxidase inhibitors (MAOIs) can cause relief or behavioral stimulation and an increase in the risk of developing postural hypotension [3]. Newer antidepressants usually have fewer or different side effects and a lower risk of toxicity than older tricyclic inhibitors and MAO inhibitors. Although drug therapy is widely prescribed for depression by doctors, less than half of the patients treated with antidepressants respond to these drugs [13]. Some patients recover partially or indirectly, and some patients are resistant to pharmacotherapy. It is therefore emphasized that there is a need to seek out new antidepressant classes. Due to the adverse effects of synthetic and chemical drugs, the use of medicinal plants, as an alternative treatment, may be relatively better, as many studies with different models have reported the positive pharmacological effects of plants in the treatment of depression [3]. In this study, depression, as well as the factors and mechanisms involved in its development, will be first addressed, and then medicinal plants and their active ingredients effective in treating depression along with their mechanisms of actions will be reported.

1.1. Biomarkers and Bio-factors Involved Depression

Various factors are involved in the development of depression (Fig. 1). Focus on the pathogenesis of depression in recent years has mainly targeted monoamine neurotransmitter disorders, decreased monoamine production, or secondary messenger system dysfunction [14]. Monoamine neurotransmitters such as serotonin (5-HT), noradrenaline, and dopamine play an important role in mediating depressive behaviors. Depression is caused by decreased function of these neurotransmitters. Monoamine oxidase-A (MAO-A) activity is one of the indicators of predisposition to mental disorders [15]. This enzyme is one of the key enzymes that are involved in the metabolism of neurotransmitters. In addition, the hypothalamic-pituitary-adrenal (HPA) axis function is impaired in patients with depression. The HPA axis is regulated by corticotropin-releasing factor (CRF). This physiological regulator plays a major role in mediating behavioral, neuroendocrine and autonomic responses to environmental stimuli. Increased CRF and hyperactivity of the HPA axis are indicative of depression [16, 17]. The levels of CRF, cortisol, and adrenocorticotropic hormone (ACTH) also increase in depressive patients [18]. There is also a relationship between adenylyl cyclase activity and major depression. Adenylyl cyclase regulates the physiological effect of drugs and hormones by producing cAMP [18]. Adenylyl cyclase activity is controlled by serotonergic receptors. In clinical trials, it has been observed that the activity of this enzyme is lower in people with depression than in those without depression [19]. One of the other factors that are involved in the pathogenesis of depression is oxidative stress. In fact, the imbalance between the production of reactive oxygen species (ROS) and the antioxidant defence system may cause or exacerbate depression [20]. Several degrees of oxidative damage and a decrease in antioxidant inhibitory enzymes have been reported in people with depression. As a result, antioxidant compounds such as acetylcysteine decrease the symptoms of depression in affected individuals [21]. Some inflammatory mediators have been reported to be involved in the development of depression in both patients and animal models, including tumor necrosis factor-alpha (TNFα) and interleukin 1 beta (IL-1β). The association between inflammation and depression has been observed in people with hepatitis C or cancer who are under TNFγ or IL-2 based immunotherapy [22]. It has also been observed that changes in the levels of tyrosine, tryptophan and phenylalanine, which indicate an amino acid metabolism disorder, are associated with depression [23]. Phenylalanine is an essential amino acid and precursor of tyrosine from which monoamine neurotransmitters such as serotonin, norepinephrine and epinephrine are derived. Tryptophan is also an essential amino acid and the precursor of serotonin. Therefore, changes in the amount of this type of amino acids are associated with depression. Impaired energy metabolism and gut microflora have also been associated with depression. In fact, depression is associated with significant changes in the biomarkers of gut microflora. Impairment in energy conversion and Krebs' cycle (tricarboxylic acid cycle) due to changes in creatinine and succinic acid disrupts energy metabolism and causes fatigue, which is one of the symptoms of the disease. The microflora-induced changes in hippuric acid and 3-indole acetic acid due to depression suggest an association between depression and gut microflora metabolism [24]. Glutamic acid and gamma-aminobutyric acid (GABA) act as

excitatory and inhibitory neurotransmitters in the mammalian brain and play an important role in mediating anxiety and depressive behaviors. Therefore, the changes in these neurotransmitters are also associated with depression [24]. In addition, Glutamate transmission inhibitors can have antidepressant effects [25].
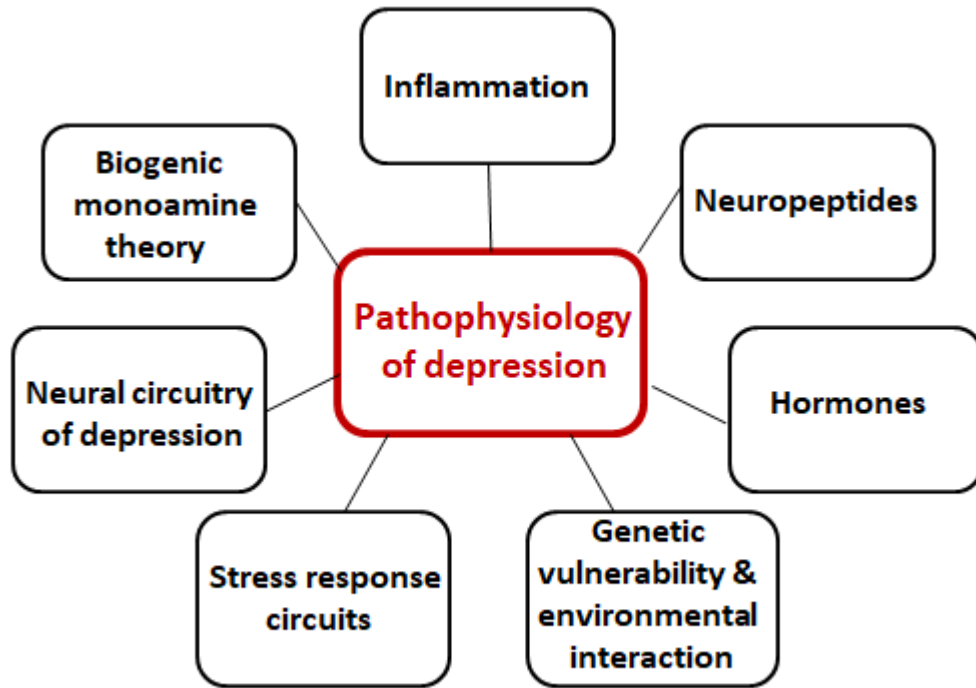
Fig. (1). The most important factors involved in depression [26].

1.2. Pharmacotherapy and its mechanisms

The development of the first antidepressant drugs, MOA inhibitors and tricyclic antidepressants in the 1950s and 1960s marked a substantial development in the treatment of depression [2]. The introduction of subsequent drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRI) such as venlafaxine, has improved the therapeutic success against depression in the past decade as much as it was with previous drugs, but with higher tolerance and fewer side effects [2]. Recently, atypical antidepressants such as bupropion, nefazodone, and mirtazapine are available to treat depression. However, the rate of recovery and the risk of disease recurrence remain high. Therefore, agents with greater efficacy and less toxicity are needed [2]. Research has shown that antidepressants exhibit inhibitory effects on the expression of inflammatory cytokines such as TNF alpha and prostaglandin E2, and the production of ROS [27]. Finally, conventional antidepressant drugs play their role by increasing monoamine levels in the synaptic cleft through at least one of the following mechanisms (Fig. 2):

1. Blocking pre-synaptic monoamine transporter increasing extracellular neurotransmitter.

2. Inhibiting MOA that destroys monoamine transmitters. Monoamine oxidase inhibitors (MAOIs) are the antidepressants that destroy the neurotransmitters serotonin, norepinephrine, and dopamine in the brain.

3. Binding to pre- or postsynaptic receptors that regulate monoamine release or its rate. It is suggested that antidepressants increase the concentration of extracellular monoamine. Depression may be caused by the lack of noradrenaline, 5-HT and dopamine in the brain at receptor sites. This argument is known as the monoamine hypothesis of depression [15]. Conventional antidepressants lead brain-derived neurotrophic factor (BDNF) toward acting as an effective antidepressant agent by increasing its level in the frontal lobe and especially the hippocampus. BDNF causes neuroplasticity that improves symptoms of depression [15].

The most common side effects of synthetic drugs are a rapid increase in the concentration of monoamine at the receptor site, which can increase anxiety and cause digestive and sexual problems [5], challenging the use of new antidepressant drugs due to late efficacy and numerous side effects. As a rich source of biologically active molecules, medicinal plants represent a promising source from which to develop new antidepressants.

1.3. Effective Medicinal Plants on Depression

Studies have shown that the desirable health effects of herbal drugs are largely due to their antioxidant properties and potential impact on cellular metabolism [28]. Medicinal plants can regulate neurotransmission by directly affecting receptors or the synthesis and distribution of neurotransmitters, or by regulating immunological processes [29]. Investigations by Rai et al [72] showed that the antidepressant effect of the active ingredients of medicinal plants was associated with neutralizing various stressors and returning monoamine receptor and neurotransmitter levels to normal and also by increasing the level of monoamine neurotransmitters in certain regions of the cortex [27, 72]. Medicinal plants and their active ingredients also produce therapeutic effects via interaction with serotonergic systems (5-HT3, 5HT2A, 5-HT1A), noradrenergic (α1 and α2 receptors) and dopaminergic (D1 and D2) receptors [30]. Medicinal plants also regulate the activity of the HPA axis and reduce CRF, ~~and~~ adrenocorticotropin and corticosterone. Some plants remove the symptoms of depression by reducing oxidative stress and inflammatory mediators. The present section addresses the overall antidepressant activity of plants.
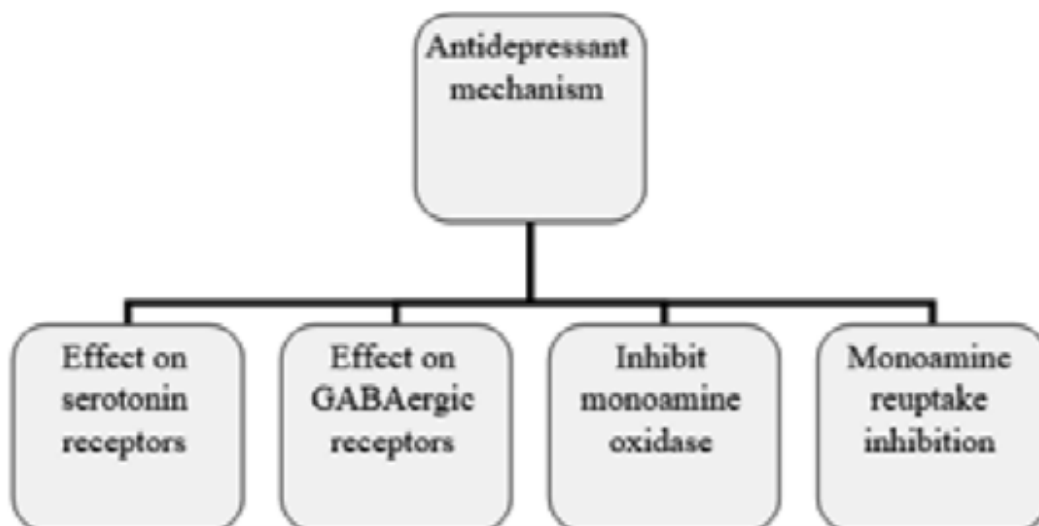
Fig. (2). Antidepressant mechanisms.

Plant-derived antidepressant phytochemicals are known to reduce the risk of certain severe disorders, including autoimmune and cardiovascular diseases, as well as neurodegenerative diseases [15]. Some herbal drugs have been approved by regulatory authorities for treating psychiatric disorders. For example, the Brazilian Health Regulatory Agency (Anvisa) has approved certain products obtained from Passiflora incarnata, Valeriana officinalis, Cimicifuga racemosa, and Piper methysticum for treating anxiety or depression. Similarly, the European Medicines Agency (EMA) has listed some plants including Hypericum perforatum L. (St. John's Wort), Melissa officinalis L. (Melissa leaf), and V. officinalis L. (Valerian Root) as being approved for the treatment of mental stress and mood disorders [31]. In these plants, well-known polyphenols such as curcumin, ferulic acid, proanthocyanidin, quercetin and resveratrol have shown potent anti-inflammatory and antioxidant properties. These phytochemicals have been frequently reported to produce neuropathic effects, which strongly indicates that they can improve symptoms of depression [15]. Table 1 shows some of the plants associated with depression.

1.4. Toxicity of Medicinal Plants

The use of medicinal plants and herbal medicines dates back in human history. Nowadays, about seventy percent of the population consume these plants for disease treatment and low toxicity although they can produce certain toxic effects [73]. Some plants are not inherently toxic, but the levels of some elements in them can be very high being sourced from environmental pollution. Fungal contamination in stored plants is a big problem, too. [74]. Although the washing process may remove toxic components, some elements such as lead and cadmium are not easily removed [75]. Most of the available medicinal plants and herbal products are not prepared industrially and do not carry the necessary information on their

packaging. Moreover, they often have not been certified and validated by a recognized body, which can concern medical practitioners as well as consumers [75]. These plants may induce a variety of toxicities in different organs of the body. In this respect, the liver and kidney are very vulnerable to herbal toxicities [76-78]. Therefore, they should be used with caution, especially for their toxic effects on kidney and liver. It should be noted that medicinal plants might also be beneficial to liver and kidneys. There are many medicinal plants, which have been shown to protect kidney or liver, or both. These plants mostly have antioxidant activity and counteract the oxidative stress induced by free radicals [79-81].

Table 1. The most important herbal medicines effective on depression and their mechanisms.

Name	Family	Model	Action mechanism(s)	Main compound(s)	Place of occurrence	Type of used extract	Reference
Epimedium brevicornum	*Berberidaceae*	CUMS	Suppressing monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) enzymes and reducing serum malondialdehyde (MDA) levels	Icariin (Flavonoid)	Asia, China and Mediterranean region		[22, 17, 32]
Chrysactinia mexicana	Asteraceae		NMDA receptor antagonist and protecting neurons against excitotoxic effects of NMDA; Increasing the division of stem cells or neuronal precursors *in vivo* and *in vitro*; Binding to the benzodiazepine binding site of GABA-A receptors and inducing pharmacological properties	Phenylpropanoids including caffeic acid, coumaric acid and ferulic acid	North America, Mexico, and some South American countries		[33, 34, 35, 36, 37]
Chamaemelum nobile	*Asteraceae/ Composit*		Apigenin present in the plant acts as a ligand of the benzodiazepine receptor; Quercetin inhibits monoamine oxidase	The flavonoids apigenin, quercetin, luteolin and terpenoid alpha, Bisabolol	Different Mediterranean regions, Europe, and temperate regions of Asia and the USA		[38, 39]
Magnolia grandiflora	*Magnoliacea*	FST, TST, CUMS	Producing effect on the serotonergic system; Regulating 5-HT, 5-HIAA, corticosterone and adenylyl cyclase.	Magnolol and honokiol	Japan and China	Aqueous	[40, 41, 32]

Name	Family	Model	Action mechanism(s)	Main compound(s)	Place of occurrence	Type of used extract	Reference
Hypericum perforatum	*Hypericaceae*	Escape deficit models, Anhedonia test, FST	A weak inhibitor of MOA; Downregulating the beta adrenergic receptors and upregulating the serotonin receptors by the extract; Changing the concentrations of neurotransmitters in certain regions of the brain; Expressing genes controlling the hypothalamic-pituitary-adrenal axis; Antioxidant defense and decreasing the inflammatory factors IL-6 and TNF-a	Hypericin, hyperforin, and isoquercetin	Western Europe, Asia, and northern Africa	Hydroalcoholic	[42, 43, 44, 44]
Lavandula angustifolia	*Lamiaceae*	FST	Increasing serotonin and gamma-aminobutyric acid, and inhibiting release of acetylcholine; Linalool through the receptors of serotonergic and noradrenergic systems.	Linalool and linalyl acetate	Mediterranean regions - Spain, France, Italy, Croatia	Aqueous	[31, 45, 46]
Salvia officinalis	*Lamiaceae*	TST, FST	The dopaminergic system	Linalool and apigenin	Oaxaca, Mexico		[45, 46, 47, 48]

Name	Family	Model	Action mechanism(s)	Main compound(s)	Place of occurrence	Type of used extract	Reference
Rosmarinus officinalis L	*Lamiaceae*	TST, FST	Monoaminergic system; Regulating tyrosine hydroxylase and pyruvate carboxylase (genes involved in GABAergic, serotonergic and dopaminergic systems).	Carnosicacid, rosmarinic acid, and luteolin Ursolic acid	Mediterranean Regions	Hexane, Ethyl acetate, Ethanolic, Aqueous	[49, 50, 51]
Danggui shaoyao San			Modulating noradrenaline and dopamine, and decreasing MDA levels and increasing superoxide dismutase (SOD) levels; Producing effect on the serotonergic system; Releasing serotonin and norepinephrine from synaptosome by paeoniflorin	albiflorin, paeonflorin, fluoric acid, ligustrazine, ligustilide and ateraacetyllinoid.	Asia		[52, 53, 54, 55, 36]
Schinus molle	*Anacardiaceae*	TST, FST	Through serotonergic, dopaminergic, and noradrenergic systems; Through increasing noradrenaline and serotonin in the synaptic cleft.	Flavonoid compounds including rutin	South America	Hexane, Ethanolic	[56, 30]

Name	Family	Model	Action mechanism(s)	Main compound(s)	Place of occurrence	Type of used extract	Reference
Glycyrrhiza glabra (Liquorice)	*Leguminosae/ Fabaceae*	TST, FST, Locomotor activity, MAO Inhibition assay	Inhibiting MOA and increasing the concentrations of serotonin, norepinephrine, and dopamine.	Glycyrrhizin	Southern Europe and parts of Asia	Aqueous, Hydroalcoholic, Ethanolic	[57, 58, 59]
Crocus sativu	*Iridaceae*	FST	Producing effect on the dopaminergic system and inhibiting norepinephrine and safranal reuptake on the serotonergic system; Increasing serotonin in the brain.	Kaempferol, Safranal, Crocin	Asia, Mediterranean and Irano-Turanian region	Aqueous, Ethanolic	[4, 60]
Borage (*Borago officinalis, Echium amoenum*)	<u>*Boraginaceae*</u>		Inhibiting 5HT reuptake; Immunomodulation	Rosmarinic acid γ-linoleic acid	Europe, in the Mediterranean region, and also in northern parts of Iran		[28, 61]
Roseroot (*Rhodiola rosea* L.)	*Crassulaceae*		Inhibiting MOA-A; modulating monoamine transmission; normalizing serotonergic transmission	Salidroside Tyrosol Rosavin	Arctic regions including Alaska, northeastern Siberia and northern parts of Europe.		[28]
Zingiber officinale (Ginger)	*Zingiberaceae*	TST, FST, Protein-ligand molecular docking	Via binding to 5-HT1A receptor	Gingerol, Shoagol	India, China, Japan, Korea, Vietnam, Europe	Hydromethanolic	[62, 63]

Name	Family	Model	Action mechanism(s)	Main compound(s)	Place of occurrence	Type of used extract	Reference
Piper methysticum	<u>Piperaceae</u>	MAO Inhibition assay	Kavalactones inhibit MAO-B Via dopaminergic mechanism and block the *in vitro* uptake of noradrenalin	Kawain, dihydrokavain, methysticin, dihydromethysticin and yangonine	South Pacific		[64, 65]
Tagetes lucida Cav.	Asteraceae	FST, Locomotor activity	Mediating effect by 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors	Quercetin gallic acid, caffeic acid	Mexico and Central America	Aqueous, Hexane, Dichloromethane, Methanolic	[66, 67]
Cimicifuga racemosa	Ranunculaceae	TST	Acting in the hypothalamus vasomotor centre. Other *in vivo* and *in vitro* studies indicate a dopaminergic effect	Triterpenes and derivatives of flavones	North America; Georgia, North to Ontario and West to Arkansas and Wisconsin	Ethanolic, Isopropanolicaqueousextracts	[68, 69]

*FST: forced swim test, * TST: tail suspension test, * CUMS: chronic unpredictable mild stress, *NMDA: N-methyl-D-aspartate

CONCLUSION

Recent pharmaceutical achievements for managing depression have not yet met with favorable clinical results. Some new and conventional drugs cause side effects. Medicinal plants provide many opportunities for the development of antidepressants. Antidepressant activities of plants are associated with various mechanisms including the HPA axis, monoamine neurotransmitters, and neurogenetic/neurotrophic factors, and their active ingredients play an important role in serotonergic, neuroadrenergic and dopaminergic systems. Hypericum, borage, and saffron exert their effects by inhibiting monoamine reuptake and roseroot and chamomile by inhibiting MOA. Hypericum produces an antidepressant effect by impacting serotonin receptors and lavender, chamomile and saffron by affecting GABAergic receptors [61]. However, the effects observed include a neurotrophic effect, such as activation of BDNF by saffron and ginseng, and neuroendocrine effects by hypericum, chamomile, and ginseng [61]. Saffron is also known as a postsynaptic NMDA receptor antagonist [61]. Studies have shown that hypericum extracts are the best registered natural treatments for mild to moderate depression. Its tolerance is good, but most important aspects are immunomodulation and pharmacokinetic and pharmacodynamic interactions. In several controlled clinical trials, saffron was shown to be more effective for mild to moderate depression than placebo and standard drugs. It is noteworthy that treatment with saffron is currently known to be the second leading herbal treatment for depressive symptoms [25, 28, 70] and in comparison with hypericum extracts, it does not cause immune system problems. Experiments on other herbal remedies such as lavender, borage, chamomile and ginseng have demonstrated antidepressant effects, but it should be emphasized that they have not yet been definitely proven [28]. Growing evidence exists suggesting the presence of an association between the antioxidant defence system and oxidative stress with the development of neuropsychiatric disorders, including anxiety and depression. Anxiety and depression have been shown to be correlated with reduced antioxidant state or enhanced oxidative stress. The available antidepressants also mostly produce their therapeutic effects, in part, by increasing antioxidant levels. Antioxidants are able to remove free radicals by scavenging them, which would further protect neuronal damage induced by oxidative stress in the brain. This may help in the remission of anxiety or depression symptoms. Understanding the functional relationship between anxiety or depression and oxidative stress might pave the way for the discovery of novel targets and the preparation of new drugs for the treatment of neuro-psychiatric disorders [71]. It should be noted that since biochemical compounds from plants are metabolized in the liver, it is essential that they are studied in clinical trials before prescription use [25]. Therefore, the acceptance of herbal drugs for the treatment of mental disorders, including depression, requires standardization of herbal extracts and isolates, adequate scientific information on their safety and efficacy, the preservation of the diversity of medicinal plants, and appropriate laws and legal regulations that should be taken into consideration in developing anti-anxiety and antidepressant drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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