REVIEW ARTICLE

The Role of Natural Products in Treatment of Depressive Disorder

Tayebeh Noori[1], Antoni Sureda[2,3], Eduardo Sobarzo-Sánchez[4,5] and Samira Shirooie[1,*]

[1]*Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran;* [2]*Research Group on Community Nutrition and Oxidative Stress (NUCOX) and Health Research Institute of Balearic Islands (IdISBa), University of Balearic Islands-IUNICS, Palma de Mallorca E-07122, Balearic Islands, Spain;* [3]*CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), 28029, Madrid, Spain;* [4]*Instituto de Investigación y Postgrado, Facultad de Ciencias de la Salud, Universidad Central de Chile; Chile;* [5]*Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago, Spain*

Abstract: Depressive disorder is one of the most common psychiatric syndromes that, if left untreated, can cause many disturbances in a person's life. Numerous factors are involved in depression, including inflammation, brain-derived neurotrophic factor (BDNF), GABAergic system, hypothalamic–pituitary–adrenal (HPA) Axis, monoamine neurotransmitters (serotonin (5-HT), noradrenaline, and dopamine). Common treatments for depression are selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, but these drugs have several side effects such as anxiety, diarrhea, constipation, weight loss, and sexual dysfunctions. These agents only reduce the symptoms and temporarily reduce the rate of cognitive impairment associated with depression. As a result, extensive research has recently been conducted on the potential use of antidepressant and sedative herbs. According to the available data, herbs used in traditional medicine can be significantly effective in reducing depression, depressive symptoms and improving patients' performance. The present study provides a summary of biomarkers and therapeutic goals of depression and shows that natural products such as saffron or genipin have antidepressant effects. Some of the useful natural products and their mechanisms were evaluated. Data on various herbs and natural isolated compounds reported to prevent and reduce depressive symptoms is also discussed.

Keywords: Depression, natural products, BDNF, HPA axis, monoamine neurotransmitters, depressive symptoms.

1. INTRODUCTION

Depression, a chronic mental disorder, affects about 15 to 20% of people in the world [1]. Today, over 300 million people around the world are depressed, which affects both social and economic aspects of their lives [2]. According to the World Health Organization (WHO), depression is recognized as a major cause of disability and a leading cause of the general burden of disease [3]. In this sense, depression has high individual and social costs leading to 50% disability-related life years [4]. Depression causes cognitive impairment and negatively affects executive function, working memory, and processing speed [5, 6]. This disease also inhibits the proper response to infection by inducing a response to type 2 helper T lymphocytes that leads to destructive and chronic inflammation [7, 8]. Inflammation plays an important role in exacerbating depression. In addition, inflammation is a physical symptom of depression and can be a cause of depression [9, 10]. Besides inflammation, other factors such as Brain-Derived Neurotrophic Factor (BDNF), GABAergic, hypothalamic–pituitary–adrenal (HPA) Axis,

monoamine neurotransmitters (serotonin (5-HT), noradrenaline, and dopamine) are involved in depression [11, 12]. Common treatments for depression are SSRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors and their effects manifest after several days and the effectiveness of these drugs is short and rarely more than 12 weeks [13, 14]. SSRIs, mostly used as the first-line treatment of depression, inhibit the reabsorption of serotonin and, by selectively acting on serotonergic systems, increase the amount of serotonin in the synapses of neurons and elongate its effect on the brain. It takes long about two weeks after taking these drugs to increase synaptic serotonin levels [15]. Unfortunately, about half of depressed patients do not respond to SSRIs [16]. Even with successful treatment for depression, there is often only relative improvement in depressive symptoms. Altogether, there is an urgent need for newer and more effective researches to treatments major depressive disorder [17]. Natural compounds can reduce the symptoms of various diseases, including depression, which attracting the attention of the scientific community and the pharmaceutical industry [18]. Therefore, this study aims to analyze the potential use of natural compounds in the treatment of depression and to study the relevant mechanisms.

*Address correspondence to this author at the Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; E-mail: shirooie@gmail.com

2. METHODS

PubMed, Scopus, and Science Direct databases with keywords such as depression, natural products, BDNF, HPA Axis, monoamine neurotransmitters were searched. All natural products effective in treating depression have been searched. Articles are considered from the earliest date to 2021. Then, all obtained articles were reviewed and according to the inclusion and exit criteria, related articles were selected to write a review article. The Google Scholar database was also searched for reliability.

3. BIOMARKERS EVALUATED IN DEPRESSION STUDIES

3.1. Inflammation

Depression, as a neurological disorder, is induced by the interaction of a wide variety of heterogeneous pathogenic mechanisms such as monoamines, genetics, and oxidative stress. It has also been shown that inflammation is one of the most relevant risk factors for major depression [19, 20]. Inflammation affects cognition through changes in the brain's signaling pattern and is associated with depression by creating a pattern of symptoms that combine in a syndrome called "disease behavior" [21]. However, the role of inflammation in the onset and recurrence of depression is still unclear [22-24]. Despite the role of inflammation in neurological, metabolic, and behavioral diseases such as depression, dementia, and metabolic disorders, these disorders simultaneously cause increased inflammation [25]. Many researchers have investigated the role of inflammatory cytokines in patients with depression. Raison *et al.* indicated that in depressed patients, the expression of inflammatory mediators is strongly increased by the activation of the toll-like receptor (TLR) signaling pathway [23]. Inflammatory markers (cytokines, chemokines) and acute phase reactants (C-reactive protein (CRP)) are also increased in the serum of major depressive patients [26-28]. Stress and depression are associated with increased production of pro-inflammatory cytokines and related products, such as interleukin-l-beta (IL-l b), interleukin-6 (IL-6), IL-6 receptor (IL-6R), and interferon-gamma (IFNy)[29]. Increased inflammation in the blood of depressive patients may indicate increased inflammatory activity in the central nervous system (CNS) and its effects on the nervous system and neurotransmitters [30]. The elevation serum concentration of the inflammatory cytokines has been demonstrated in depressed patients [31, 32]. An increase in pro-inflammatory cytokines could indicate the potential appearance of future depression [33]. Chronic inflammation related to chronic diseases, such as rheumatoid arthritis, allergies, aging-related diseases, and, perhaps, MDD, may be modulated by some proteins encoded by clock genes that may affect the development of chronic inflammatory diseases or increase the severity of their symptoms. It has been indicated that agomelatine as the first melatonergic antidepressant, agomelatine relieves chronic inflammation by restoring circadian rhythms and acting on such clock genes and circadian inconsistencies, often seen in MDD [34]. Confirmation of the association between inflammation and depression shows that inflammation has an indirect effect on mental health. Inflammatory agents may be involved in depression by activating indolamine-2,3-dioxygenase (IDO) [35].

This enzyme converts tryptophan to quinornineo (KYN), which can increase the risk of neurological processes and neurotoxicity [36]. Thus, IDO is involved in depression by reducing tryptophan as a precursor of serotonin. It should be noted that not all depressed patients show an increased inflammation. Increasing inflammatory markers are associated with unusual symptoms (obesity, metabolic syndrome) of depression [37-39]. Serotonin-noradrenalin antidepressants venlafaxine and mirtazapine may influence cytokine secretion in patients affected by MD, restoring the equilibrium between their physiological and pathological levels and leading to recovery [40].

3.2. Brain-derived Neurotrophic Factor (BDNF)

Some studies have proposed a relation between neurotrophins and mood disorders. Brain-derived neurotrophic factor (BDNF) is the most representative neurotrophin associated with depression [41]. Recently, its role in several processes in the adult brain, such as synaptic plasticity, has been suggested [42, 43]. The effect of BDNF on the pathophysiology of several psychiatric disorders and the mechanism of action of psychotropic drugs have also been proven [44-48]. Martinotti *et al.* have shown that Agomelatine increases BDNF expression in the prefrontal cortex and hippocampus as well as the expression of activity-regulated cytoskeleton - associated protein in the prefrontal cortex. Acute agomelatine treatment modulates BDNF expression by interacting with melatonergic MT1/MT2 and serotonergic 5-HT2C receptors. Prolonged treatment with agomelatine increases neurogenesis in the hippocampus, particularly *via* enhancement of neuronal cell survival, reducing stress-induced glutamate release in the prefrontal/frontal cortex [49]. There is a link between BDNF signaling and various neurotransmissions disorders such as schizophrenia and depression [50, 51]. Midbrain dopamine neurons in animals may be destroyed by impaired BDNF mRNA expression, which indicates the sensitivity of dopamine cells to BDNF mRNA synthesis [52]. According to *in vitro* studies, BDNF, through regulation of dopamine D1 and D5 receptors in striatum astrocytes is effective in improving the survival of dopamine neurons [52]. It could also be effective in D3 receptor signaling by controlling the expression of a specific dopamine gene in the adult brain. BDNF is also effective in regulating the function of dopaminergic neurons in the limbic system and can play a role in causing behavioral sensitivity by controlling the expression of D2 and D3 receptors [50]. Increased BDNF expression is involved in the differentiation of dopaminergic neuronal morphology in the striatum [53]. There is a significant reduction in the number and size of neurons in the cortex [54], hippocampus [55], and dorsal thalamus [56] in the brains of depressed patients. Simultaneously, elevated levels of BDNF are related to a decrease in white matter neurons and the distribution of synapses and dendrites [57, 58].

3.3. GABAergic System

Gamma aminobutyric acid (GABA) was discovered in the brain in 1950 and was introduced in 1967 as an inhibitory neurotransmitter. GABA is now recognized as the major inhibitory neurotransmitter in the vertebrate brain [59]. Various studies have shown that the GABAergic system plays an important role in the coordination of local neural networks,

communication in brain areas and their function [60, 61]. Therefore, studying the components of this system is very important in understanding how different parts of the brain coordinate and the mechanism of neurological disorders and disorders [62, 63]. Depression is associated with age, and there is evidence that age-related pathologies cause GABAergic dysfunction [56, 64, 65]. According to the GABAergic defect hypothesis, depressive disorders lead to a decrease in GABA concentration in the brain and changes in the expression and function of its receptors, as well as changes in GABAergic transmission by chloride homeostasis [66]. It has been shown that the GABAergic neurotransmitter system is decreased in the brains of depressed patients resulting in altered signal integrity of the cortex and hippocampus [66-68]. Brain imaging and magnetic resonance spectroscopy confirm the reduction of GABAergic neurotransmission and GABA content in the prefrontal and occipital cortex of depressed patients [67].

3.4. Hypothalamic -Pituitary -Adrenal (HPA) Axis

The hypothalamic–pituitary–adrenal (HPA) axis has been implicated in the pathophysiology of a variety of mood and cognitive disorders. Neuroendocrine studies have demonstrated the HPA axis overactivity in major depression [69]. Moreover, a relationship of HPA axis activity with cognitive performance and a potential role of HPA axis genetic variation in cognition has been suggested [69]. The HPA axis is one of the main biological systems involved in the stress of the body and the CNS. According to evidence, HPA activity is higher in healthy people than in depressed people [70, 71]. There is a direct relationship between depressive disorders and impaired HPA axis regulation. Therefore, it can be concluded that dysfunction of the HPA axis leads to depression. Risk factors for depression include early life trauma and recurrent psychological stress characterized by HPA-based hyperactivity [72-74]. Modulation of HPA-based activity may be effective in the biological response to antidepressants. Therefore, one of the most effective and important strategies in the production of antidepressants can be to target HPA activity-based abnormalities [73, 75, 76]. In depressed patients, high levels of HPA activation lead to high production of the glucocorticoid hormones, which, in turn, reduce neuronal survival [75]. According to human and animal studies, the stress in the early stages leads to a change in the activity of the HPA axis in response to stress in adulthood and predisposes a person to depression [77, 78].

3.5. Lateral Habenula (LHb)

The lateral habenula (LHb) is a brain region that is important in the pathophysiology of depression. This region is activated by negative experiences and its role in coding negative signals has been proven [79]. Hyperactivity of neurons in this area coincides with depressive symptoms [80]. The increased metabolic and synaptic activity of LHb neurons has also been demonstrated in models of depressed rodents, such as those learned from helplessness and resulting from chronic stress [81, 82]. By increasing the activation of the LHb nucleus, the connected serotonergic, noradrenergic, dopaminergic systems are inhibited and the HPA axis is stimulated [83-86]. By inhibiting the activity of LHb neurons, analgesic agents such as morphine can produce analgesic effects [87]. The LHb response to depression and pain is

the same pathological changes. Also, due to the functional and morphological relationships of LHb with the central regions of the brain, LHb is involved in the processing of emotional reactions and pain [88-90].

3.6. Monoamine Neurotransmitters (Serotonin (5-HT), Noradrenaline, and Dopamine)

Recently, in the pathogenesis of depression, the focus has been moved on monoamine neurotransmitter disorders, decreased monoamine production, or secondary messenger dysfunction. Among the factors involved in mediating depressive behaviors are monoamine neurotransmitters such as 5-HT, noradrenaline, and dopamine [11]. As a regulator of neurons, serotonin is involved in neuroplasticity in the early stages of brain development. In mature adult brains, some of these functions remain active. One of the important pathophysiological mechanisms in depression is serotonergic imbalance. Significant atrophy in the prefrontal cortex, hippocampus, thalamus, and basal ganglia has also been reported in depressed patients [91]. The role of serotonin in enhancing the polysilicate form of nerve cell adhesion molecule (PSA-NCAM) has been observed. PSA-NCAM has a significant effect on synaptogenesis and neurite regeneration [92, 93]. The role of serotonin in the regulation of the physiological processes, such as sleep, appetite and mood has been proven in several studies [94, 95]. Therefore, one of the most important goals in the treatment of mental disorders such as major depression and anxiety is the serotonergic system [96]. One of the important factors in the pathophysiology of bipolar disease (BD) is noradrenaline. As noradrenaline increases, depression in BD improves but can increase the risk of manic change in BD [97]. Therefore, in the treatment of major depression, short-term treatment of increased adrenaline can be effective in improving BD [98]. These hypotheses confirm the role of noradrenaline in the pathophysiology of BD as well as manic disorder. Therefore, the antidepressant effects and change of mania by noradrenaline are important issues in the field of BD. Three important actions are involved in increasing of noradrenaline: 1) elevation noradrenaline *via* preventing the reuptake of noradrenaline in the synaptic cleft, 2) monoamine oxidase inhibitors (MAOIs) prevent the inactivation of noradrenaline, 3) by blocking the α2 receptor, the release of noradrenaline is prevented [98].

The most abundant catecholamine in the mammalian brain is dopamine (DA), which plays an important role in the coordination of movement, endocrine function, reward, mood, memory and emotions [99]. Dopamine plays an important role in the pleasure deficits of depression [100]. Impaired central dopaminergic neurotransmission is associated with depression, which is associated with impaired regulation of DA release or changes in the expression or function of DA receptors (DARs) [101]. The complex dopaminergic activity is influenced by the regulation of numerous brain structures, such as the ventral subiculum of the hippocampus and the basolateral amygdala. Despite the results of various studies that show the effect of dopaminergic system defects in depression, these defects are probably due to dysregulation of order-dependent circuits [100]. It is hypothesized that there is a direct link between dopamine involvement in major depression and the dopaminergic mesolimbic reward pathway [102].

3.7. Natural Products

According to the results of studies, the antioxidant properties of natural products and their effect on cellular metabolism have caused plants to have beneficial effects on health [103, 104]. Natural products can regulate neurotransmission in a variety of ways, including *via* affecting receptors or synthesizing and distributing neurotransmitters or by regulating immune processes [11, 105]. The results of a study showed that the active ingredients in medicinal plants through neutralizing various stressors, returning monoamine receptor and neurotransmitter levels to normal and also rising the level of monoamine neurotransmitters in certain parts of the cortex lead to antidepressant effects [106, 107]. Medicinal plants and their active compounds in a variety of ways, including interaction with serotonergic systems (5-HT3, 5HT2A, 5-HT1A), noradrenergic (α1 and α2 receptors) and dopaminergic receptors (D1 and D2), exert their therapeutic effects [108]. It should be noted that natural products are involved in regulating HPA-based activity and reducing CRF and adrenocorticotropin and corticosterone. Several natural products are able to relieve the symptoms of depression through decreasing oxidative stress and inflammatory mediators [11]. See Table **1**.

3.8. Apigenin
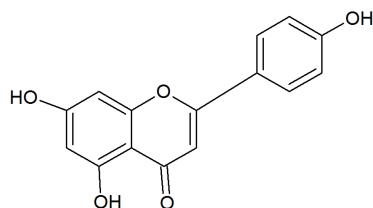
Apigenin (4, 5, 7-trihydroxyflavone) is a natural flavonoid mainly present as a glycosylated form in citrus fruits with antioxidant, anticancer, antioxidant and, anti-inflammatory properties [109-112]. Several studies have shown that apigenin exerts antidepressant activity through the promotion of different anti-inflammatory pathways, including p38 mitogen-activated protein kinases (p38/MAPK) and phosphoinositide-3-kinase–protein kinase B/Akt (PI3K/Akt) [113] and the overexpression of γ-receptors activated by peroxisome and expression levels of serum BDNF [109, 114]. The results of an *in vivo* study indicated that apigenin at 40 mg/kg dose has antidepressant properties *via* up-regulation of brain-BDNF levels in the mice hippocampus [114]. Ruipeng Li *et al.*, in an *in vivo* study, using a mice model, reported that apigenin has antidepressant effects by inhibiting inflammatory cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) expression through modulating nuclear factor κB (NF-κB) activation in a model of lipopolysaccharides (LPS)-induced depression in mice [115]. Another *in vivo* study showed the antidepressant effects of apigenin at a dose of 60 mg/kg by promoting autophagy through the adenosine monophosphate-activated protein kinase mammalian target-of-rapamycin (AMPK/mTOR) pathway in mice subjected to restraint stress [116]. The findings of Yi *et al.*, indicated that apigenin improved the abnormality in the central monoaminergic neurotransmitter, HPA axis, and activity systems of adenylyl cyclase in the chronic mild stress (CMS) depressed rats, as well as reduced serum corticosterone-induced CMS increase [117]. According to behavioral experiments, apigenin is in-volved in increasing sucrose function and decreasing immobility time. Mice treated with corticosterone and apigenin also reduced BDNF levels in their hippocampus. Therefore, due to the role of corticosterone and apigenin in the regulation of BDNF, their antidepressant effects have been emphasized [113].

3.9. Baicalin
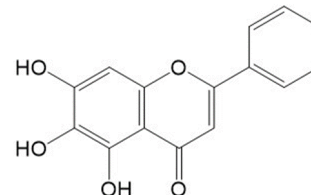
Baicalin is a flavonoid compound extracted and refined from the dried roots of *Scutellaria baicalensis*, which has a variety of effects, including antioxidant, anti-inflammatory and neuroprotective effects [118, 119]. The antidepressant effect of baicalin in the rat model of chronic unpredictable mild stress (CUMS) depression has been proven in several studies [120, 121]. Baicalin exerts neuroprotective and anti-inflammatory effects through the modulation of several pathways, such as AMPK [122] and PI3K/Akt [123, 124]. Baicalin is effective in improving anxiety / depression-like behaviors and is involved in the development of hippocampal neurogenesis [125]. Baicalin is involved in reducing depressive-like behavioral changes, expressing tyrosine kinase (TrkB) receptors by acting on synaptophysin (SYP), activating the Rac1-cofilin pathway, and improving synaptic plasticity [126]. Baicalin has been reported to have a similar antidepressant-like activity in the CUMS model, affecting the N-methyl-D-aspartate receptor / NR2B-extracellular signal-regulated kinase 1/2 (NMDAR / NR2B-ERK1/2) and calmodulin-dependent protein kinase II (CaMKII) signaling pathways. Therefore, baicalin can act as an antidepressant and neuroprotective agent and can be effective in the inhibition of oxidative stress and neuroinflammation [127]. According to Wang *et al.*, baicalin is effective in reducing learning and memory impairment due to cerebral ischemia/reperfusion and is also able to eliminate depressive behaviors caused by chronic mild stress [128, 129] . The results of a study by Yu *et al.*, [130] also showed that baicalin inhibits neuronal apoptosis in mice exposed to CUMS [131].

3.10. Berberine
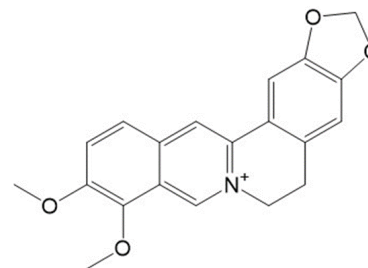
Berberine is a natural isoquinoline alkaloid found in plants such as European and Oregon grapes [132] and as herbal medicine is effective in the cure of mood disorders [133, 134]. Berberine can inhibit the activities of the pro-oxidant enzymes lipoxygenase and xanthine oxygenase involved in the production of reactive oxygen species (ROS) [135]. This action

Table 1.   **Some of the natural products and their mechanisms in depression.**

Effective Material	Source	Mechanism	Dose	*In Animal/In vivo* Model	Type of Disease	Potency	References
Apigenin	Citrus fruits	Up-regulation of BDNF	40 mg/kg	Male ICR mice	Depression-like behavior induced by chronic corti-costerone treatment	Strong	[114]
		Inhibition of inflam-matory cytokines, iNOS and COX-2 expression *via* the modulation of NF-kB activation	50 mg/kg	Male ICR mice	LPS-induced depres-sion	Strong	[115]
Baicalin	*Scutellaria baicalensis Georgi (Huangqin)*	Inhibits both oxida-tive stress and neu-roinflammation	25 and 50 mg/kg	C57BL/6 male mice	Chronic mild stress-induced depression	Strong	[127]
		Prevents neuron apoptosis and AMPK receptor expression	20, 40 mg/kg	Male SD rats	Chronic mild stress-induced depression	Moderate	[131]
Berberine	European bar-berry, Oregon grape	Influence on BDNF-eEF2 pathway in the hippocampus, and CREB signaling in the frontal cortex	10.0 mg/kg	Female ICR mice	Depression in ovari-ectomized mice	Strong	[137]
		Targeting miR-34b-5p and miR-470-5p and Overexpression BDNF	20 mg/kg	Male C57BL/6J mice	Chronic mild stress-induced depression	Strong	[138]
Curcumin	*Curcuma longa*	Inhibition of mono-amine oxidase A and B enzymes	10-80 mg/kg	Male Laca mice	Depression	Strong	[149]
Folic acid		Prevented IL-6,Effects on the modulation of HCY, BDNF and β-EP	0.8 mg/kg	Male Sprague-Dawley (SD)	Chronic mild stress-induced depression	Strong	[158]
Genipin	*Gardenia jas-minoides ElLis*	Elevation of 5-HT and NA levels in the brain, regulation of BDNF, increases mRNA and protein	25, 50 and 100 mg/kg	Male Sprague Dawley rats	Chronic mild stress-induced depression	Moderate (50 and 100 mg/kg), Strong (25 mg/kg)	[170]

| Effective Material	Source	Mechanism	Dose	*In Animal/In vivo* Model	Type of Disease	Potency	References
Genistein	Soy	Enhances the antide-pressant effect of amitriptyline	10 mg/kg	Male albino mice (BALB/c strain)	Depression	Moderate	[179]
		Improves the quality of life and depression symptoms in osteo-penic postmenopau-sal women	54 mg	Clinical trial	Depression in post-menopausal women	Strong	[173]
Luteolin	Celery, green pepper	Inhibits iNOS, COX-2, TNF-α, IL-1β, NO, PGE2 Blocks NF-κB acti-vation	20 μM	BV2 murine microglia	Neuroinflammation	-	[182]
N-acetylcysteine	Amino acid cysteine	Inhibits the expres-sion and secretion of IL-10, inflammatory cytokines (*e.g.*, IL-1b and IL-6)	15 mM	THP-1 cells	LPS-activated mac-rophages	-	[264]
		Via anti-inflammatory poten-tial and restoring serotonergic respons-es in the stressed rat	25, 50, and 100 mg/kg	Male Wistar rats	Chronic mild stress-induced depression	Moderate (50 mg/kg), Strong (100 mg/kg)	[204]
Naringenin	Citrus fruits (grape fruit, oranges	Effects on neuro-chemical and neuro-endocrine activity, elevation of hippo-campal GR and monoamine neuro-transmitters, reduc-tion of serum corti-costerone	5, 10, 20 mg/kg	Male ICR mice	Depression	Moderate (5 mg/kg), Strong (10 and 20 mg/kg)	[205]
		Restores corti-costerone levels in serum and antioxi-dant enzymes (Cata-lase, SOD GSH), nitrite and MDA in cerebral cortex and hippocampus	25, 50 and 100 mg/kg	BALB/c male mice	Olfactory bulbecto-mized-mice model of depression	Moderate (25 mg/kg), Strong (50 and 100 mg/kg)	[208]

(Table 1) contd….

Effective Material	Source	Mechanism	Dose	*In Animal/In vivo* Model	Type of Disease	Potency	References
Piperine	Black pepper (*Piper nigrum Linn*.) and long pepper (*P. longum* Linn.),	Increases BDNF expression in the hippocampus	5, 10 mg/kg	Male ICR mice	Corticosterone-induced depression	Strong	[210]
		Inhibits of oxidative stress and HPA axis hyperactivation	1μM	PC12 cells	Depression	-	[214]
Quercetin	Apples, straw-berries, soy-beans	Reduced neuroin-flammation through the modulation of BDNF and iNOS	100 mg/kg	Sprague-Dawley rats	LPS-induced depres-sion	Strong	[225]
		Alleviates impair-ment of learning and memory with regulat-ing the BDNF-related imbalance expression of Copine 6 and TREM1/2 in the hippocampus and the PFC	40 mg/kg	Sprague-Dawley rats	LPS-induced depres-sion	Strong	[226]
Epigallocate-chin-3-O-gallate	Green tea	Protects neurons against inflammation in hippocampus	50 mg/kg	Male Wistar rats	chronic mild stress-induced depression	Strong	[230]
		Prevents decreases in BDNF levels, and normalized HPA axis dysregulation, inhib-its IL-1b and TNF-α in the hippocampus, modulation of the HPA axis and bio-synthesis of neuro-steroids	25 mg/kg	Sprague-Dawley rats	Post-traumatic stress disorder	Strong	[231]
Resveratrol	Skins of red grapes, red wine, Japanese knotweed, and some nuts	Rectifying the stress-based HPA-axis dysfunction para-digm and upregula-tion of hippocampal BDNF expression	80 mg/kg	Male Swiss albino mice	Corticosterone-induced depression	Strong	[240]
		Enhanced neurogen-esis, upregulated Sirt1, and inhibited NF-kB activation	20 mg/ kg	Male C57/BL6 mice	LPS-induced depres-sion	Strong	[242]

(Table 1) contd….

Effective Material	Source	Mechanism	Dose	*In Animal/In vivo* Model	Type of Disease	Potency	References
Rosmarinic acid	*Rosmarinus officinalis*	Upregulates pyruvate carboxylase and tyrosine hydroxylase	50, 100 mg/kg	Male ICR mice, PC12 cells	Depression	Strong	[246]
		HPA axis activation modulation, MKP-1 downregulation, BDNF upregulation, and an increase in dopamine level in the brain	5 and 10 mg/kg	Male ICR mice	Depression	Moderate (5 mg/kg), Strong (10 mg/kg)	[248]
		Restores BDNF and pERK1/2 protein expression	10 mg/kg	Male Sprague–Dawley (SD)	chronic mild stress-induced depression		[243]
Saffron *(Crocus sativus L.)*	-	Reduction of beck depression and anxiety inventory scores	50 mg	Randomized controlled trial	Depression and anxiety	Strong	[263]
		Effects on the neurotrophin, BDNF	10, 12.5, 25, and 50 mg/kg	Male Wistar Albino rats	Depression	Strong	[262]

evidences the antioxidant properties of berberine, which is related to its neuroprotective effect against cognitive disorders. Moreover, berberine is involved in the modulation of neurotransmitters and their receptors in the CNS [134]. The results of an *in vivo* study have shown that berberine (10, 20 mg/kg) reduces immobility time during the forced swimming test (FST) and the tail suspension test (TST) in the mice [130]. As the level of BDNF increases, the antidepressant effects of berberine become apparent. The anti-depressant effects of berberine have also been evidenced in an ovariectomy model of depression by affecting the BDNF-eEF2 pathway in the hippocampus and cAMP Response Element-Binding Protein (CREB) signaling in the frontal cortex [136, 137]. In the study by Zhan *et al.*, berberine was able to inhibit the depressive behaviors of CUMS mice and increase the growth of hippocampal neurons by targeting miR-34b-5p and miR-470-5p. Similarly, BDNF also targets miR-34b-5p and miR-470-5p. Through overexpression, BDNF can help regulate depressive behaviors in CUMS mice and promote the growth of hippocampal neurons [138].

3.11. Curcumin
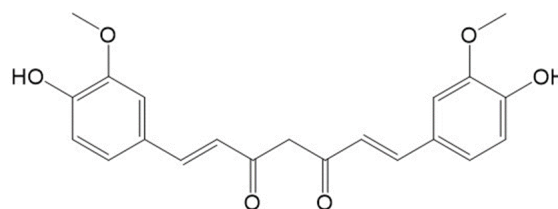
Curcumin is a polyphenolic compound derived from the plant *Longa curcuma* [139]. The pharmacological effects of this natural flavonoid include antioxidant [140], anti-inflammatory [141], antitumor [142], anti-diabetic [143], cardioprotective [144], hepatoprotective [145], and protection against ischemic/reperfusion injury [146]. In addition to improving various neurological disorders, curcumin has strong anti-inflammatory, anti-amyloid and neuroprotective activities [147]. The inhibition of monoamine oxidase enzymes (MAO) A and B [148], modulation level of the neurotransmitters in the brain, increase of BDNF levels [149, 150] and anti-inflammatory effects are among the antidepressant

mechanisms of curcumin [149, 151] Considering the mono-amine hypothesis, a decrease in monoamine neurotransmit-ters can induce depression [150, 152]. According to *in vitro* and *in vivo* studies, curcumin can reduce depression by in-creasing the concentration of monoamines available to inter-act with receptors, like tricyclics [149, 153]. Curcumin, as the MAOI A and B, has an effective role in modulating sero-tonin and dopamine [154]. One of the effective mechanisms of curcumin in reducing depressive symptoms is the suppres-sion of transcription signaling pathways such as NF-κB. This mechanism is essential in the production of proinflammatory cytokines (such as IL-6 and IL-1b) and the pathogenesis of inflammation [155].

3.12. Folic Acid
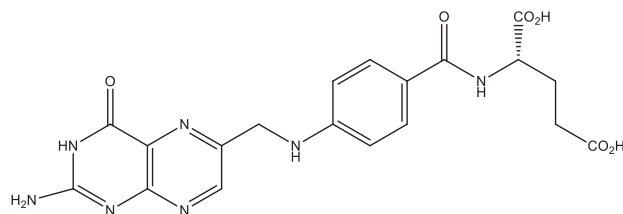
Folic acid is a water-soluble vitamin known as vitamin B$_9$ commonly reduced in depressed people [156]. One of the most effective ways to prevent and treat folate deficiency is folic acid supplementation. Therefore, knowing the source of folic acid is important to reduce the risk of neurological problems, such as depression [148, 157]. Since folic acid is necessary for the appropriate biosynthesis of the monoamine neurotransmitters, the supplementation with this vitamin could act as an antidepressant [158]. There is a relationship between depression and a low level of FA. Decreased folic acid results in decreased dopamine, norepinephrine, and ser-otonin, resulting in a neurochemical diathesis for depression [159]. In the study conducted by Bender *et al.*, the relation-ship between folic acid levels in depressed patients and healthy individuals were investigated. The results showed that depressed people had lower serum FA levels than those in healthy people. Depressed people also consumed less fo-late, and serum folate levels were lower in depressed patients [159]. It has been proved folic acid supplementation is effec-tive in restoring the final function of pancreatic beta cells, and glucose is involved in insulin secretion. FA administra-tion is effective in restoring the normal function of beta cells in fluoxetine-treated cells [160]. In one study, the admin-istration of FA to mice with chronic stress improved them. Folic acid inhibits the release of CUMS-induced IL-6 by increasing dopamine and norepinephrine in serum and brain tissue and is involved in the modulation of HCY, BDNF, and β-EP [158].

3.13. Genipin
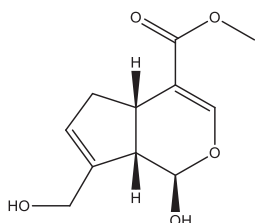
Gardenia jasminoides J.Ellis fruit has been used to treat inflammation, headache, edema, fever, liver disorders and hypertension. The active ingredient in G. *jasminoides*, the iridoid glycoside geniposide, is broken down into genipin when it enters the body through β-glucosidase [161]. Gen-ipin has also been shown to be useful in treating depression in rodent models [162-164]. Genipin also has other func-tions, including anti-inflammatory, anti-angiogenic, anti-thrombotic, anti-diabetic, antioxidant, protection of neural activity, inhibition of nitric oxide production and anti-tumor, regulation of epinephrine and 5-hydroxytryptamine levels in the hippocampus and energy metabolism [165-168]. Genipin probably exerts its effect by modulating the monoaminergic neurotransmitter system and regulating the post-receptor pathway, particularly at 5-HT1AR, 5-HT2AR, and BDNF levels in the hippocampus [169, 170]. In one study, the forced swim test (FST) and the tail suspension test (TST) showed the positive effect of genipin in reducing depression in mice [162]. The study by Wang *et al.*, revealed that gen-ipin exerts its antidepressant effect in a manner similar to antidepressants by increasing levels of 5-HT and noradrena-line and affecting serotonergic (5-HT1A and 5-HT2A recep-tors) and monoaminergic neurotransmitter systems in the rat brain. BDNF regulation is also performed by genipin [170].

3.14. Genistein
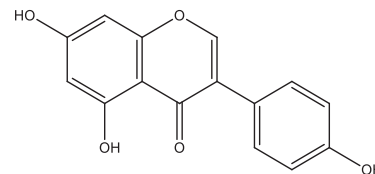
Genistein is a dietary isoflavone mainly present in soy-beans, with therapeutic effects against cancer, osteoporosis, cardiovascular disease and depression [171, 172]. Various results suggested the role of genistein in improving quality of life and reducing depressive symptoms in postmenopausal women with osteoporosis [173, 174]. However, the mecha-nism of action of genistein in depression is not known. New-ly, the role of microRNA on the pathophysiology of depres-sion and the performance of depression therapies has been considered [175-177]. In one study, oral and long-term ad-ministration of genistein in mice had a similar function to antidepressants. The effects of genistein on the 5-HT system coupled with 5-HT1A receptors are suggested to mediate the antidepressant activity [178]. One *in vivo* study reported a similar effect of genistein and antidepressants, with effects comparable to amitriptyline (10mg/kg) [179]. The inhibitory effect of genistein on MAO has also been demonstrated [180]. According to a clinical trial study, daily consumption of 54 mg isoflavone genistein, along with calcium and vita-min D3 for 2 years in osteopenic postmenopausal women, improved quality of life and depressive symptoms [173].

3.15. Luteolin
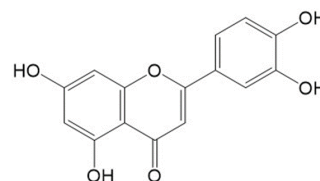
Luteolin is a flavonoid present in plants such as celery, green pepper, leaves and, seeds of perilla with diverse therapeutic effects including anti-inflammatory, anti-anxiety and memory enhancing; luteolin freely penetrates into the brain [181, 182]. Luteolin exerts beneficial effects mainly through its antioxidant properties deactivating oxygen and nitrogen species. Since possible stimuli that cause nerve damage include oxidative stress and neuroinflammation, chemical groups that have antioxidant and anti-inflammatory activity such as luteolin can be useful in the treatment of neurological diseases [183]. Luteolin also inhibits cytokine expression, NF-kB, and TLR4 signaling in immune cells such as mast cells [184, 185]. In addition, luteolin attenuates microglial activity and shows BDNF-like behavior *in vitro* and *in vivo* studies [186, 187]. Luteolin is implicated in decreased microglial activity, mast cell-mediated allergic inflammation, and impaired BDNF signaling [188]. Luteolin prevents the expression of iNOS, COX-2, TNF-α, and IL-1β as well as NO and prostaglandin E2 (PGE2) production induced by LPS. In addition, luteolin blocks the activation of NF-kB derived from LPS exposure [182].

### 3.16. N-acetylcysteine (NAC)
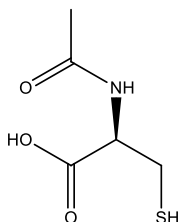
N-acetylcysteine (NAC) is a synthetic N-acetyl derivative and multifunctional drug, the precursor of reduced glutathione (GSH) and, has been widely used as an antioxidant drug [189]. NAC is used to treat psychiatric disorders [190, 191], depressive symptoms [192], bipolar depression [193], depressive behavior in Huntington's disease [194], diabetes-induced depression-like behavior and oxidative stress [195], cognitive dysfunction in depression [196], anxiety and oxidative damage due to unpredictable chronic stress in zebrafish [197]. NAC is thought to help decrease alcohol-related neuroinflammation in mice and alcohol withdrawal anxiety [163]. Consumption of NAC in mice, alcohol abstinence-induced depressive-like behavior, reduced depressive symptoms. The properties of NAC in the treatment of depression can be attributed to the effects of NAC on monoaminergic neurotransmitters and its anti-inflammatory effects [163, 198]. It should be noted that the antioxidant and anti-inflammatory properties of NAC have been proven in some studies [199, 200]. The antidepressant and antianhedonic effects of chronic administration of NAC have also been observed in animal models similar to imipramine *via* elevation of brain SOD activity and antioxidant capacity [201, 202]. NAC also inhibits the expression and secretion of inflammatory cytokines (*e.g.*, IL-1b and IL-6) and IL-10 with anti-inflammatory properties in LPS-activated macrophages under mild oxidative conditions and, consequently, could be effective in treating major mental disorders [203]. The beneficial effect of NAC in the treatment of depression in CUMS-exposed mice may be due to its anti-inflammatory potential and the restoration of serotonergic responses [204].

3.17. Naringenin
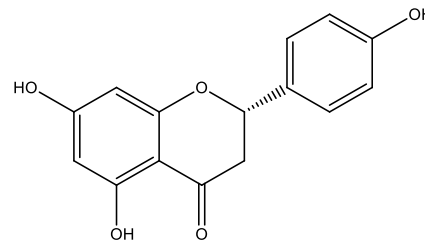
Naringenin (5, 7, 4-trihydroxy flavanone) is the most abundant flavonoid in *Solanum Lycopersicum*, citrus (grapefruit, orange), *Mentha aquatica* and flowers of *Acacia podalyriifolia*. Naringenin has antidepressant properties since it is involved in restoring serotonin and noradrenaline levels in the brain and HPA axis dysfunction [205, 206]. Probably, naringenin by inhibiting neural activity and monoamine oxidase prevents oxidative nerve damage and thus reduces central nervous system disorders, including depression [207]. According to an *in vivo* study, the therapeutic effects of mandarin antidepressant-like drugs are exerted through mechanisms such as effects on neurochemical and neuroendocrine activity, increased glutathione reductase (GR) in hippocampus and monoamine neurotransmitters and, decreased serum corticosterone [205]. Naringenin is able to reduce serum corticosterone levels, increase antioxidant enzymes (catalase, superoxide dismutase (SOD)), GSH and nitrite and reduce MDA levels in the cerebral cortex and hippocampus, evidencing stress and antioxidant healing properties. Naringenin also reduces pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, NF-kB signaling pathway and increases neurotrophic growth factors such as BDNF [208]. In addition, in an *in vivo* study naringenin was found to restore the altered levels of tryptophan, serotonin, 5-hydroxy-indole acetic acid, and quinornine in the hippocampus and cortex of BALB/c male mice [208].

3.18. Piperine
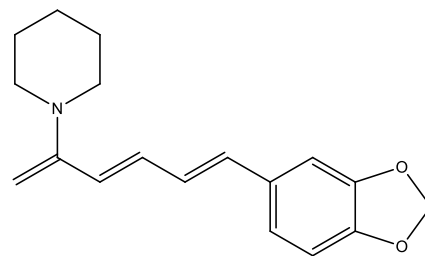
Piperine, a major alkaloid of black pepper (*Piper nigrum* L) and long pepper (*P. longum* L), has been extensively used as condiment and flavoring for all types of savory dishes [209]. It has been shown that the antidepressant effect of piperine in corticosterone-treated rats may be due to increased BDNF expression in the hippocampus [210]. Studies have also suggested the role of piperine as an anti-depressant by inhibiting MAO activity, increasing brain levels of monoamine neurotransmitters in mice [211, 212]. In addition, piperine exerts its antidepressant effects by regulating the serotonergic system [209, 213] and inhibiting oxidative stress and HPA axis hyperactivity [214]. Administration of piperine to treat depression results in corticosterone-induced changes in BDNF expression. This suggests a possible role

for BDNF in the treatment of depression. In another study, piperine has a protective effect against corticosterone-induced neurotoxicity in mouse pheochromocytoma (PC12) cells, which may be due to inhibition of oxidative stress and regulation of BDNF mRNA levels [214, 215]. The anti-inflammatory and neuroprotective properties of piperine help prevent the ischemia of cerebral ischemia [216]. Altogether, the antioxidant, anti-inflammatory and neuroprotective properties of piperine play a role in the antidepressant effects of piperine [217, 218].

3.19. Quercetin
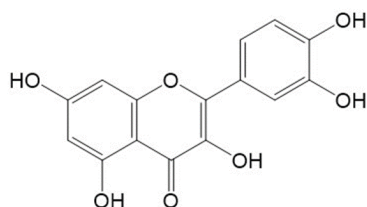
Quercetin (3,3′,4′,5,6-pentahydroxyflavone) is a polyphenol abundant in strawberries, apples, soy, grapes, broccoli, tea and, citrus fruits [219]. Quercetin has anti-allergic, anti-rheumatic, anti-inflammatory and, anti-viral properties [220]. Quercetin has recently been shown to be effective in protecting against stress and depression behaviors and ameliorating memory in male mice [221]. Quercetin has also been reported to reduce stress and plasma cortisol levels [222], improve memory function [223] and reduce anxiety and depression-like behaviors [224]. The results of a study showed the role of quercetin in reducing inflammation by modulating BDNF and iNOS, which improved anxiety-like symptoms. Therefore, it is concluded that quercetin is effective in improving psychological behaviors and neurochemical changes as symptoms of anxiety [225]. Quercetin reduced LPS-induced depressive behaviors and learning and memory impairment by regulating the BDNF-associated expression of Copine 6 and TREM1 / 2 in the hippocampus and prefrontal cortex of rats [226].

3.20. Epigallocatechin-3-O-gallate (EGCG)
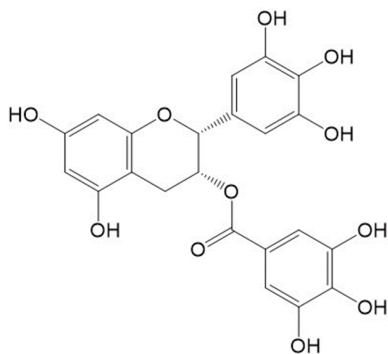
Epigallocatechin-3-O-gallate (EGCG) is catechin with powerful antioxidant activity abundant in green tea [227]. This compound is useful in the treatment of inflammation [228]. EGCG can reduce radiation-induced abnormalities and protect against DNA damage and apoptosis in the hippocampus [229]. Due to the effect of EGCG in inhibiting neuroinflammation and thus, reducing depression, it can act as an antidepressant. This compound is effective in balancing the excess NO produced by CUMS. It has been revealed that

the presence of large amounts of NO synthesized by the enzyme nNOS may lead to neuronal cell death and the production of reactive NO species [230]. The results of the study by Lee *et al.*, led to the hypothesis of improved memory and behavioral deficits by the EGCG. The administration of EGCG resulted in a significant improvement in cognitive and memory dysfunction and amelioration of BDNF levels decrease in rats subjected to single prolonged stress (SPS) [231]. EGCG can inhibit proinflammatory cytokines such as IL-1b and TNF-α in the hippocampus. It has also been shown that EGCG can treat stress by modulating the HPA axis and neurosteroid biosynthesis [231].

3.21. Resveratrol
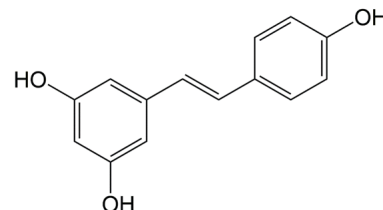
Resveratrol (3, 5, 40-trihydroxyacetylbene) is available as a phytoalexin and polyphenol in the skin of red grapes, red wine, Japanese knots and some nuts [232]. Resveratrol has antioxidant, anti-inflammatory, anti-apoptotic, and anti-tumor properties [233-235]. Resveratrol is also a neuroprotective compound that can prevent damage to nerve cells and glial cells [236]. Resveratrol also improves brain-related behavioral factors related to learning, anxiety, depression, and memory by regulating brain function [237, 238]. Resveratrol as a dopamine antagonist in the treatment of depression can increase the neurotransmitters dopamine and serotonin in the prefrontal cortex and the expression of neuropeptide Y (NPY) in the brain [239]. According to behavioral and biochemical assays in a corticosterone-rat model of depression, the treatment with resveratrol has been shown to act as an antidepressant agent. This effect may be mediated through improving the stress-based HPA-axis dysfunction paradigm and upregulation of hippocampal BDNF expression [240]. Chen *et al.*, showed that resveratrol has a significant effect on improving LPS-induced depression and mitochondrial oxidative stress in the hippocampus of mice [241]. The Finding of a study demonstrated that resveratrol, through increasing neurogenesis, regulating Sirt1 and, inhibiting NF-κB activation, leading to improving depression [242].

3.22. Rosmarinic Acid
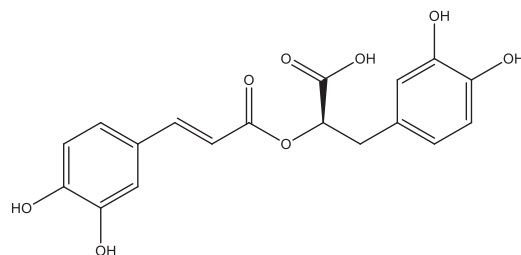
Rosmarinic acid is one of the most relevant biologically active compounds of *Rosmarinus officinalis* [243]. Rosmarinic acid has therapeutic properties such as anti-inflammatory, anti-oxidative stress, anti-aging, liver and,

heart protection. Some studies have also indicated beneficial effects in depressed animal models [243-245]. It has been reported that rosmarinic acid is involved in the regulation of two enzyme genes associated with the regulation of GA-BAergic, serotonergic and dopaminergic pathways namely pyruvate carboxylase (PC) and tyrosine hydroxylase (TH). Its anti-depressant effect has also been proven *via* controlling cholinergic and monoaminergic performance in *in vivo* and *in vitro* studies [246, 247]. Results of the research by Shinji *et al.*, showed that rosmarinic acid is capable of modulating HPA axis activation, downregulating mitogen-activated protein kinase phosphatase 1 (MKP-1), overregulating BDNF, and increasing dopamine levels in the brain leading to improvements in TST-induced depressive mice [248]. According to *in vivo* studies, rosmarinic acid can treat depressive behaviors caused by chronic anxiety and restore BDNF and pERK1 / 2 protein expression [243, 249, 250]. It has been indicated that rosmarinic acid, in addition to neurotrophic properties, can improve cholinergic functions associated with the ERK1 / 2 and MAPK signaling pathway in PC 12 cells. Rosmarinic acid also regulates serotonergic, GABAergic and dopaminergic pathways by regulating PC and TH [246].

3.23. Saffron (*Crocus sativus* L.)

Saffron (*Crocus sativus* L.) and some of its constituents, including crocin, crocetin and, safranal are effective against mental disease *via* several neurological mechanisms [123, 251, 252]. Probably, crocin by inhibiting reabsorption of dopamine and norepinephrine, and safranal by inhibiting serotonin reuptake are involved in the saffron antidepressant effects [253]. Saffron and its active components, like other chemical antidepressants have antidepressant properties but with fewer complications and side effects [254]. The antidepressant effect of saffron is mediated by the modulation of the levels of certain chemicals in the brain, such as serotonin, [255, 256] or acting as an anti-MAO [257]. The components of saffron have antioxidant and anti-inflammatory properties and are also able to regulate the expression of BDNF and the HPA axis [258]. In addition, modulation of pathways related to neurotransmitters, immune regulation, anti-inflammation and anti-oxidative stress is among the properties of saffron and its constituent compounds that have been reported in animal models [258]. An *in vivo* study has shown that the administration of saffron extract increases dopamine concentrations and glutamate levels in a dose-dependent manner [259] . The results of a study showed that obsessive behaviors induced by non-selective serotonin receptor agonist meta-chlorophenylpiperazine in mice were improved by crocin administration *via* modulating serotonergic activity [255]. Animal studies have shown that saffron regulates HPA-based activity *via* lowering plasma corticosterone levels [260, 261]. Studies also confirm the effects of crocin as a neuroprotective agent has positive effects on neurotrophin and BDNF [262]. The results of Mazidi *et al.*, evidenced the positive effect of saffron in patients with anxiety and depression, suggesting that the administration of saffron for 12 weeks caused a significant improvement in these patients [263].

CONCLUSION

Depression is a well-known multifactorial neuropsychiatric disorder with a significant prevalence. Although various treatments have been proposed so far, they are associated with poor treatment outcomes and serious side effects. Recent studies have shown the role of serotonin, dopamine, noradrenaline, BDNF, GABAergic, HPA Axis and, inflammation in the onset and progression of depression. Evidence suggests that increasing the use of natural compounds may be an alternative strategy to delay the appearance and progression of depression and depressive-like symptoms. In particular, some studies have shown that natural bioactive compounds may be used as effective agents in the treatment of depression. However, randomized and placebo-controlled trials are necessary to confirm the potential of these compounds as a possible treatment for this debilitating disorder.

AUTHORS' CONTRIBUTIONS

SS contributed to the conception of the manuscript. SS, TN, ESS and AS drafted the manuscript. Finally, all of the authors critically revised the manuscript and gave the final approval.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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