Advances in the Preclinical Study of Some Flavonoids as Potential Antidepressant Agents

León Jesús German-Ponciano,1 Gilberto Uriel Rosas-Sánchez,1 Eduardo Rivadeneya-Domínguez,2 and Juan Francisco Rodríguez-Landa1,2,3

1Programa de Doctorado en Neuroetología, Instituto de Neuroetología, Universidad Veracruzana, Xalapa, VER, México
2Facultad de Química Farmacéutica Biológica, Universidad Veracruzana, Xalapa, VER, México
3Laboratorio de Neurofarmacología, Instituto de Neuroetología, Universidad Veracruzana, Xalapa, VER, México

Correspondence should be addressed to Juan Francisco Rodríguez-Landa; juarodriguez@uv.mx

Received 25 August 2017; Revised 11 December 2017; Accepted 24 December 2017; Published 1 February 2018

Academic Editor: Marie-Aleth Lacaille-Dubois

Copyright © 2018 León Jesús German-Ponciano et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Flavonoids are phenolic compounds found commonly in plants that protect them against the negative effects of environmental insults. These secondary metabolites have been widely studied in preclinical research because of their biological effects, particularly as antioxidant agents. Diverse flavonoids have been studied to explore their potential therapeutic effects in the treatment of disorders of the central nervous system, including anxiety and depression. The present review discusses advances in the study of some flavonoids as potential antidepressant agents. We describe their behavioral, physiological, and neurochemical effects and the apparent mechanism of action of their preclinical antidepressant-like effects. Natural flavonoids produce antidepressant-like effects in validated behavioral models of depression. The mechanism of action of these effects includes the activation of serotonergic, dopaminergic, noradrenergic, and γ-aminobutyric acid-ergic neurotransmitter systems and an increase in the production of neural factors, including brain-derived neurotrophic factor and nerve growth factor. Additionally, alterations in the function of tropomyosin receptor kinase B and activity of the enzyme monoamine oxidase A have been reported. In conclusion, preclinical research supports the potential antidepressant effects of some natural flavonoids, which opens new possibilities of evaluating these substances to develop complementary therapeutic alternatives that could ameliorate symptoms of depressive disorders in humans.

1. Introduction

Depression is one of the most frequently diagnosed psychiatric disorders in the general population, the symptoms of which negatively impact health and are associated with high financial costs [1]. According to the World Health Organization, depression will become the primary cause of disability by 2030 [2].

A wide variety of antidepressant drugs are available to treat the symptoms of depression. Such antidepressants produce their therapeutic effects through actions on diverse neurotransmitter systems, including the serotonergic, noradrenergic, and dopaminergic systems [3]. The principal antidepressant drugs are tricyclic antidepressants (e.g., clomipramine and imipramine), monoamine oxidase inhibitors (e.g., phenelzine and selegiline), selective serotonin reuptake inhibitors (e.g., fluoxetine and fluvoxamine), selective dopamine reuptake inhibitors (e.g., amineptine and methylphenidate), selective norepinephrine reuptake inhibitors (e.g., reboxetine and viloxazine), and dual antidepressant drugs (e.g., venlafaxine and duloxetine) [4, 5].

Most antidepressant drugs have a delayed onset of therapeutic actions and many have side effects when taken in the long term. This has led patients to search for alternatives, based on the use of plants with reputed antidepressant activity [6]. An increasing number of studies have investigated natural chemical compounds with potential antidepressant activity [7], including bioactive metabolites, such as flavonoids, that exert multiple effects on the central nervous system [8].

Substantial preclinical evidence indicates that some flavonoids reduce behavioral endophenotypes of depression in animal models by increasing the concentrations of different...
neurotransmitters and expression of neurotrophic factors in the brain [9, 10]. The present review focuses on the results of preclinical research that indicate the potential antidepressant effects of some flavonoids and describes the mechanisms of action that are involved in these effects. We propose future scientific research in the area of pharmacotherapy to develop safe and effective antidepressant drugs based on natural products to ameliorate the symptoms of depression in humans.

2. Background on Flavonoids

Flavonoids are phenolic compounds that are widely distributed in vascular plants. Many chemical compounds, both in their free form and in the form of glycosides, have been evaluated to determine their biological activity [11]. More than 5000 types of flavonoids have been identified, which are structurally different and possess a wide range of biological activities. Flavonoids are chemical compounds with a low molecular weight whose base structure (Figure 1) comprises a system of rings of diphenyl pyrene or phenyl benzopyrene accompanied by two variable groups of hydroxyl phenolic radicals [12].

According to the chemical structure of flavonoids (Figure 2), they can be classified as flavonoids, flavones, flavanones, isoflavones, and anthocyanidins [62]. Studies in mammals and in vitro have shown that flavonoids exert antioxidant, antiallergic, hepatoprotective, antiviral, anticarcinogenic, neuroprotective, antitoxic, anxiolytic, antiepileptic, estrogenic, and antidepressant-like effects by inhibiting some enzymes [63–66], which is dependent on the dose and type of flavonoid administered.

3. Flavonoid Metabolism

The daily dietary intake of flavonoids in humans is approximately 1-2 g per day, principally depending on individual alimentary habits [67]. Most flavonoids are found in plants in the β-glycoside form. After intake, the processes of hydrolysis occur, but since the union-β in these sugars is resistant to the hydrolysis produced by pancreatic enzymes, this metabolic process occurs in the intestinal lumen through actions of the lactase phlorizin hydrolase that is located in the membrane of enterocytes. When phlorizin hydrolase hydrolyzes flavonoids, they become capable of crossing intestinal membranes through passive diffusion. Another enzyme that facilitates the hydrolysis of flavonoids is cytosolic β-glycosidase, which hydrolyzes a high number of glycosides [68, 69]. Cytosolic β-glycosidase is located intracellularly in erythrocytes; therefore, active transport is required to cross cellular membranes. It is produced by sodium-glucose transport protein, which depends on sodium (SGLT-1) [69].

Hydrolyzed flavonoids (aglycones) are conjugated through methylation, sulphatation, and glucuronidation. Because of their high conjugation, hydrolyzed flavonoids are detected in low concentrations in plasma [70]. For example, hesperetin aglycone (the active form of the flavonoid hesperidin) is metabolized by the cytochrome isoforms P450 CYP1A and CYP1B1. This first-pass metabolism principally occurs through intestinal cells [71]. The metabolites of hesperidin/hesperetin are eliminated by renal route. Their metabolites are found in urine but not feces, suggesting that the high bacterial degradation of phenolic acids occurs at the level of the colon, allowing passage to the systemic circulation [71]. Particularly, the elimination of the flavonoid chrysin depends on the outflow, in which conjugated structures are hydrolyzed through sulphatases and glucuronidases in the intestine, suggesting that chrysin has low intestinal absorption, in which it is detected in high concentrations in feces [72].

Some studies have shown that hydrolyzed flavonoids and their conjugated derivatives may cross the hematoencephalic barrier and exert actions on the central nervous system [73]. This may at least partially explain their multiple pharmacological actions at the neuronal level that affect cognition and emotional and affective states. Numerous preclinical studies have shown that some flavonoids reduce depressive-like behavior, and these effects are related to the activation of neurotransmitter systems and trophic factors in the brain.
### Table 1: Plants with antidepressant-like effects associated with their total flavonoids content.

| Plant (family) | Doses (animal) | Duration of treatment | Behavioral test | Reference |
|---------------|---------------|-----------------------|-----------------|-----------|
| *Alpinia oxyphylla* Miq. (Zingiberaceae) | 10 mg/kg, p.o. (A) | 14 days | FST, SPT | [13] |
| | 400 mg/kg, p.o. (B) | Single dose | TST | [14] |
| *Hemerocallis citrina* L. (Xanthorrhoeaceae) | 10, 20, and 40 mg/kg, p.o. (C) | 35 days | SPT | [15] |
| *Apocynum venetum* Linn. (Apocynaceae) | 0.35 mM/kg, i.p. (B) | Single dose | FST, TST | [16] |
| *Hibiscus esculentus* L. (Malvaceae) | 500 and 750 mg/kg, i.p. (D) | Single dose | FST, TST | [17] |
| *Apocynum venetum* L. (Apocynaceae) | 50 and 100 mg/kg, p.o. (E) | 10 days | FST, TST | [18] |
| *Glycyrrhiza uralensis* Fisch. (Fabaceae) | 30, 100, and 300 mg/kg, p.o. (F) | 28 days | FST, TST | [19, 20] |
| *Byrsonima crassifolia* (L.) Kunth (Malpighiaceae) | 500 mg/kg, p.o. (E) | Single dose | FST | [21] |
| *Cecropia pachystachya* Trécul (Urticaceae) | 50 mg/kg, p.o. (G) | 8 days | FST | [22] |
| *Chrysactinia mexicana* A. Gray (Asteraceae) | 1, 5, 10, 100, and 200 mg/kg, p.o. (H) | Single dose | FST | [23] |
| *Opuntia ficus-indica* (L.) Mill. (Cactaceae) | 30 mg/kg, p.o. (E) | 14 days | FST, TST | [24] |
| *Hibiscus rosa-sinensis* Linn. (Malvaceae) | 30 and 100 mg/kg, p.o. (C) | Single dose | FST, TST | [25] |
| *Actaea spicata* L. (Ranunculaceae) | 200 mg/kg, p.o. (I) | Single dose | FST | [26] |
| *Clerodendrum serratum* Linn. (Verbenaceae) | 25 and 50 mg/kg, p.o. | 7 days | FST, TST | [27] |

(A) Male Kunming mice; (B) male mice; (C) male Sprague-Dawley rats; (D) male Swiss albino mice; (E) male ICR mice; (F) rats; (G) male Wistar rats; (H) male Swiss Webster mice; (I) male LACA mice. FST: forced swim test; TST: tail suspension test; SPT: sucrose preference test.

### 4. Antidepressant-Like Effects of Flavonoids in Plant Extracts

The treatment of depressive disorders is principally based on the use of synthetic antidepressant drugs (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and dual-action antidepressants) that are clinically effective but produce side effects. A principal limiting factor in the use of antidepressant drugs is their delayed onset of therapeutic antidepressant effects. Generally, therapeutic effects in humans occur after 2-3 weeks of treatment through neuronal plastic changes and the modification of neurotransmitter receptors. This process requires a relatively long time to produce antidepressant effects [74, 75]. In the first weeks of antidepressant treatment, patients may experience a worse mood state compared with their state before the initiation of pharmacological treatment [76]. Patients have sought therapeutic alternatives to ameliorate symptoms of depression. Infusions or standardized extracts of plants have been used for the alternative treatment of depression [77]. However, in most cases, these alternative therapies have not been investigated in systematic studies to support or refute their purported medicinal properties. Such a dearth of studies can pose a health risk to patients. Preclinical studies have evaluated the effects of plant extracts that contain a high percentage of total flavonoids (Table 1) that produce antidepressant-like effects in animal models of depression through actions on neurotransmitter receptors and production of neurotrophic factors in the brain [40].

Behavioral models (e.g., tail suspension test, forced swim test, and chronic unpredictable mild stress [CUMS] paradigm) allow identification of the potential antidepressant effects of diverse natural substances as flavonoids [78, 79], among others. Naringenin (10, 20, and 50 mg/kg), an isoflavone isolated from citrus peel, reduced total immobility time in the tail suspension test in male mice, similar to the effects of 20 mg/kg fluoxetine, a clinically effective antidepressant drug. These effects were interpreted as potential antidepressant-like effects [52]. Interestingly, this effect was blocked by pretreatment with p-chlorophenylalanine methyl ester (100 mg/kg) and α-methyl-p-tyrosine (100 mg/kg), inhibitors of the synthesis of serotonin and norepinephrine, respectively [52]. This suggests that the mechanism of action of naringenin involves the activation of serotonergic and noradrenergic neurotransmitter systems in the brain. Additionally, 10 and 20 mg/kg naringenin increased the
expression of brain-derived neurotrophic factor (BDNF) in the hippocampus after 21 days of treatment in mice that were subjected to CUMS [28], which was associated with an antidepressant-like effect. These results indicate that the antidepressant-like effect of naringenin may be mediated by the activation of both neurotransmitter systems and neurotrophic factors. Such mechanisms of action have also been identified for other clinically effective antidepressant drugs, such as fluoxetine [80].

Park et al. (2006) [81] found that a standardized extract of *Cirsium japonicum* Fisch. ex DC (Asteraceae) produced antidepressant-like effects in male mice. This effect was replicated in subsequent studies that evaluated the antidepressant-like effect of an extract of this plant at doses of 50, 100, 200, and 400 mg/kg and its principal chemical constituents (i.e., linarin, pectolinarin, chlorogenic acid, and luteolin) at doses of 10 mg/kg in the forced swim and open field tests [30]. The authors showed that the antidepressant-like effects of this plant extract were produced by the flavonoid luteolin through actions on the GABA\_A receptor. Such GABA\_A receptor activation has also been involved in the antidepressant-like activity of other plant metabolites [82, 83] and some neurosteroids such as allopregnanolone [84–86].

In male Sprague-Dawley rats, CUMS and an acute injection of corticosterone were used to produce depression-like behavior. The antidepressant-like effects of the flavonoid icariin (60 mg/kg), isolated from *Epimedium brevicornum* Maxim (Berberidaceae) on depression-like behavior produced by CUMS or corticosterone injection, were evaluated in the forced swim test. Corticosterone and CUMS increased total immobility time, reflecting despair-like behavior, and reduced BDNF concentrations in the hippocampus. These effects were prevented by the administration of icariin flavonoid, which was associated with the antidepressant-like effect [32].

A preclinical study of the methanolic extract of *Byronima crassifolia* (L.) Kunth (Malpighiaceae) at a dose of 500 mg/kg reported an antidepressant-like effect that was similar to the clinically effective antidepressant imipramine in albino ICR mice in the forced swim test. The authors indicated that this antidepressant-like effect was attributable to flavonoids in the extract [21], corresponding to quercetin (1.4 mg/kg), rutin (4.4 mg/kg), and hesperidin (0.7 mg/kg), which produce antidepressant-like effects when they are individually injected [9, 54, 87, 88]. Additionally, it has been reported that the administration for 7 days of flavonoid quercetin (10, 50, and 200 mg/kg, p.o.) decreases the 5-hydroxyindole acetaldehyde production modulating the serotonergic system by attenuating mitochondrial MAO-A activity in the brain [89], which is involved in the therapeutic effect of some antidepressant drugs.

Oral administration of 25, 50, and 100 mg/kg of a standardized aqueous extract, referred to as *Xiaobuxin-Tang*, which contains four different natural products (i.e., *Haematitum, Flos Inulae, Folium Phyllistachydis Henonis*, and *Semen Sojae Preparatum*), reduced immobility time in both the forced swim and the tail suspension tests in lipopolysaccharide-treated ICR mice, thus demonstrating an antidepressant-like effect. *Xiaobuxin-Tang* also reduced the levels of proinflammatory cytokines in the brain [90], apparently by its high content of flavonoids. A reduction of immobility time in the forced swim test was also produced by acute or chronic administration of 30, 100, and 300 mg/kg of aqueous [91] or ethanolic [92] extracts of *Melissa officinalis* L. (Lamiaceae). This same effect was produced by its active metabolite rosmarinic acid (36 mg/kg) in male Sprague-Dawley rats [91], and the authors suggested that the antidepressant-like effect of this extract could be associated with its high content of rosmarinic acid, which is able to modulate the serotonergic system [91]. However, it is not possible to discard the participation of other chemical constituents of the *M. officinalis* extracts in their antidepressant-like effects, considering the high content in essential oils and flavonoids such as quercitrin, apigenin, and luteolin derivatives that may inhibit monoamine oxidases A (MAO-A) activity and interact with the GABA\_A receptors [93], which also occurs with the majority of the conventional antidepressant drugs [94].

*Glycyrrhiza uralensis* Fisch. (Fabaceae) is another plant with potential antidepressant-like effects that are associated with its content of at least five flavonoids (i.e., liquiritin, liquiritigenin, isoliquiritigenin, isoononin, and 7,4’-dihydroxyflavone). An extract of this plant inhibited the production of tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) in microglial cells in mice [95]. These findings are important because TNF-\(\alpha\) has been detected in high concentrations in patients with anxiety and depression symptoms. Therefore, a reduction of TNF-\(\alpha\) could be beneficial for ameliorating symptoms of anxiety and depression, as is the case with other antidepressant agents. The flavonoid isoliquiritigenin also inhibits TNF-\(\alpha\) and increases the concentration of BDNF in the hippocampus and cerebral cortex [95]. Administration of the flavonoid 5,7-dihydroxyflavone (chrysin) at doses of 1 and 10 mg/kg for 60 days increased BDNF concentrations in the hippocampus and prefrontal cortex [96] and produced antidepressant-like effects in the forced swim test in mice [10]. These data are relevant because higher plasma and brain concentrations of BDNF were detected when clinically effective antidepressant drugs were administered in experimental animals (for review, see [97]) and depressed patients (for review, see [80]), suggesting that flavonoids have a similar pharmacological profile as conventional antidepressant drugs.

Su et al. (2014) [98] evaluated the effects of the Chinese herbal formula *Xiao Chai Hu Tang*, which contains parts from plants described as Radix Bupleuri Chinensis, Radix Scutellariae Baicalensis, ginseng, Rhizoma Pinelliae Ternatae, Radix Glycyrrhiza Uralensis, Rhizoma Zingiberis Recens, and Fructus Jujubae. This herbal preparation contains a high percentage of flavonoids, glycosylated flavonoids, and saponins. The authors tested the effects of administration of 0.6, 1.7, and 5 mg/kg for 4 weeks. The extract was administered in male Sprague-Dawley rats subjected to CUMS, and the effects were evaluated in the open field test; glucose preference and consumption and food consumption were also evaluated. The results showed that CUMS reduced glucose preference and food consumption, reflecting anhedonia, which is a principal symptom in depressed patients. Interestingly, these deleterious effects of CUMS were prevented by the
Antidepressant-Like Effects of Flavonoids Isolated from Plants

Flavonoids produce pharmacological actions on the central nervous system (Table 2) to regulate emotional and mood states associated with plastic and neurochemical changes as is the case with conventional antidepressant drugs [9, 10, 38, 101]. Preclinical studies have also reported the potential antidepressant-like effects of specific flavonoids (Table 3). Hesperidin is a flavonoid that has different pharmacological actions (e.g., antioxidant, antineoplastic, and neuroprotective effects) in vitro and in vivo. This flavonoid has been studied as a potential antidepressant agent because of its actions on the serotonergic, dopaminergic, and noradrenergic systems. The administration of 0.1, 0.3, and 1 mg/kg hesperidin (i.p.) for 21 days in Swiss mice significantly reduced total immobility time in the tail suspension test. This antidepressant-like effect was associated with a significant increase in BDNF concentrations in the hippocampus [9] and actions at the 5-HT1A receptors [106]. Also, the administration of 10, 20, and 40 mg/kg astilbin (i.p.) for 21 days in male C57BL/6J mice exerted antidepressant-like effects in the forced swim test, tail suspension test, and CUMS paradigm, and these effects were associated with an increase in BDNF concentrations in the cerebral cortex. These effects were similar to those produced by 10 mg/kg of the tricyclic antidepressant imipramine [34].

The behavioral and molecular effects of the flavonoid baicalein (40 mg/kg, i.p., for 14 days) were evaluated in male Sprague-Dawley rats. Baicalein significantly reduced total immobility time, similar to the antidepressant fluoxetine, in the forced swim test. This antidepressant-like effect was associated with activation of the dopaminergic system and greater expression of BDNF mRNA in the hippocampus, an effect also detected with the antidepressant fluoxetine [35]. In support, injections of baicalein (1, 2, and 4 mg/kg, i.p., for 21 days) in male Kunming mice subjected to CUMS reduced immobility time in the forced swim and tail suspension tests, which was accompanied by an increase in extracellular signal-regulated kinase and BDNF expression in the hippocampus, similar to 15 mg/kg of the antidepressant imipramine [36].

Another flavonoid, baicalin, isolated from the dried root of Scutellaria baicalensis Georgi (Labiateae), produces an antidepressant-like effect in the forced swim and tail suspension tests in mice treated with 25 and 50 mg/kg, p.o. This effect was similar to that produced by 20 mg/kg of the antidepressant fluoxetine. Apparently, the baicalin effect was associated with inhibition of monoamine oxidase enzymes types A and B [107], a mechanism of action involved in the therapeutic effect of some antidepressant drugs.
| Flavonoid          | Doses                        | Treatment duration | Effects                                                                                                                                   | Reference |
|-------------------|------------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Naringenin        | 5, 10, and 20 mg/kg          | 21 days            | Increase in BDNF concentrations in the hippocampus in male mice                                                                          | [28]      |
|                   | 5, 10, and 20 mg/kg          | 14 days            | Increase in 5-HT, DA, and NE in the hippocampus in male ICR mice                                                                       | [29]      |
|                   | 10 mg/kg                     | 30 min before test | Increases in chloride ion flow at the GABA<sub>A</sub> receptor in male rats                                                            | [30]      |
| Luteolin          | 50 mg/kg                     | 23 days            | Attenuation of the expression of endoplasmic reticulum stress-related proteins in the hippocampus in male ICR mice                      | [31]      |
| Icariin           | 60 mg/kg                     | 21 days            | Increases in BDNF concentrations in the hippocampus in male rats                                                                        | [32]      |
|                   | 0.01, 0.1, 0.3, and 1 mg/kg  | 21 days            | Increase in BDNF and NGF concentrations in the hippocampus in male C57BL/6 mice                                                        | [33]      |
| Hesperidin        | 50 mg/kg                     | 13 days            | Increase in BDNF concentrations in the hippocampus in male C57BL/6 mice                                                                | [34]      |
| Astilbin          | 10, 20, and 40 mg/kg         | 21 days            | Increase in BDNF concentrations in the cerebral cortex in male mice, similar to imipramine                                               | [35]      |
|                   | 10, 20, and 40 mg/kg         | 14 days            | Increase in dopamine and BDNF concentrations in the hippocampus in male rats                                                            |           |
| Baicalein         | 1 and 4 mg/kg                | Single injection or 21 days | Restoring of the reduction of extracellular signal-regulated kinase phosphorylation and BDNF expression in the hippocampus of male Kunming mice subjected to CUMS | [36]      |
|                   | 5 and 20 mg/kg               | 28 days            | Increase in BDNF concentrations in the hippocampus and prefrontal cortex in female mice                                                | [37]      |
| Chrysin           | 5 and 20 mg/kg               | 14 days            | Increase in 5-HT and BDNF concentrations in the hippocampus in male C57B/6J mice                                                         |           |
|                   | 5, 10, and 20 mg/kg          | 60 min before test | Activation of the serotonergic system, apparently through inactivation of MAO-A enzyme in male mice                                      | [38]      |
| Fisetin           | 5 mg/kg                      | 14 days            | Increases in phosphorylated TrkB (pTrkB) in the hippocampus in male ICR mice                                                           | [39]      |
| Orientin          | 20 and 40 mg/kg              | 21 days            | Increase in BDNF, serotonin, and norepinephrine concentrations in the hippocampus and prefrontal cortex in male mice                    | [40]      |
| 7,8-Dihydroxyflavone | 1, 3, and 10 mg/kg          | 60 min before test | Increase in BDNF concentrations in the hippocampus and prefrontal cortex in male mice                                                   | [41]      |
| Icariin           | 20 and 40 mg/kg              | 35 days            | Decrease in oxidative stress and neuroinflammation in the hippocampus in male rats                                                      | [42]      |
| Dihydromyricetin  | 10 and 20 mg/kg              | 7 days             | Increase in mRNA for BDNF in the hippocampus in male C57BL/6 mice                                                                     | [43]      |
| Silymarin         | 100 and 200 mg/kg            | 14 days            | Increase in 5-HT, DA, NE, and BDNF concentration in the hippocampus and cerebral cortex, similar to fluoxetine in adult Wistar rats    | [44]      |
| Myricitrin        | 10 mg/kg                     | 21 days            | Increases in cell proliferation in the subgranular zone of the hippocampal dentate gyrus in male BALB/c mice                             | [45]      |
| Myricetin         | 50 mg/kg                     | 21 days            | Increases in BDNF concentrations in the hippocampus in male C57BL/6 mice                                                               |           |
| 3,5,6,7,8,3'<sub>1</sub>,4'<sub>1</sub>-Heptamethoxyflavone | 50 and 100 mg/kg | 15 days            | Increase in BDNF concentration, neurogenesis, and neuroplasticity in the hippocampus in male C57BL/6 mice                              | [47, 48] |
The administration of 10, 20, 30 mg/kg of the flavonoid vitexin (p.o.) also significantly reduced total immobility time in both the forced swim and the tail suspension tests. Interestingly, animals treated with vitexin exhibited a significant increase in the time spent climbing in the forced swim test [53], suggesting that activation of the noradrenergic system may be involved in the antidepressant-like effect of this flavonoid. A selective increase in the time spent climbing is only produced by antidepressant drugs that act on the noradrenergic system [108]. Injections of the serotonin 5-HT\textsubscript{1A} receptor antagonist 1-(2-methoxyphenyl)-4-(4-[2-phthalimido]butyl)-piperazine (NAN-190) or dopamine receptor antagonist SCH23390 blocked the antidepressant-like effect of vitexin [53], indicating that the antidepressant-like effects involve the activation of at least two neurotransmitter systems (i.e., serotonergic, noradrenergic, and dopaminergic). Similarly, the flavonoid nobiletin (25, 50, and 100 mg/kg, p.o.), isolated from citrus peels, produces antidepressant-like effects in the forced swim and tail suspension tests in male ICR mice. Interestingly, these effects are blocked by previous injection of WAY 100635 (a serotonin 5-HT\textsubscript{1A} receptor antagonist), cyproheptadine (a serotonin 5-HT\textsubscript{2A} receptor antagonist), prazosin (an \(\alpha_1\)-adrenoceptor antagonist), SCH23390 (a dopamine D\textsubscript{1} receptor antagonist), or sulpiride (a dopamine D\textsubscript{2} receptor antagonist), showing that the antidepressant-like effect of nobiletin involves participation of serotoninergic, noradrenergic, and dopaminergic systems [109], as is the case as well with bioflavonoid apigenin in several brain structures [59]. This multiple mechanism of action is unsurprising. The administration of standardized herbal products or phytomedicines prepared with Hypericum perforatum L. (Hypericaceae) extracts activates multiple neurotransmitter systems and produces both preclinical and clinical antidepressant effects [110–112]. However, these multiple actions have been associated with some severe side effects [113]. Further studies are necessary to explore the multiple actions of flavonoids in the brain under different experimental conditions (e.g., acute or chronic treatment) to identify potential side effects to ensure consumer safety.

Other flavonoids with antioxidant, anti-inflammatory, and neuroprotective effects have also been evaluated as potential antidepressant agents, one example of which is the flavonoid fisetin. The administration of 10 and 20 mg/kg fisetin (i.p.) significantly reduced total immobility time in the forced swim and tail suspension tests [38]. This antidepressant-like effect was apparently produced by activation of the serotonergic system. The blockade of serotonin synthesis by pretreatment with \(p\)-chlorophenylalanine blocked the antidepressant-like effect of fisetin. This study also found that fisetin inhibited the activity of MAO-A, which is involved in the metabolism of serotonin and norepinephrine [38]. Similarly to other flavonoids, fisetin seems to exert its antidepressant-like effects through at least two different mechanisms of action: activating the serotonergic system and inhibiting monoamine metabolism. However, other neurotransmitter systems could be involved in the antidepressant-like effect produced by flavonoids. Two synthetic flavones, 3’-methoxy-6-methylflavone and 3’-hydroxy-6-methylflavone, in doses of 100 mg/kg, i.p., produce antidepressant-like effects in the forced swim and tail suspension tests, similar to antidepressant imipramine [114]. Interestingly, the effect produced by both synthetic flavonoids was partially ameliorated by coadministration of bicuculline (a competitive \(\gamma\)-aminobutyric acid binding site antagonist), suggesting the modulation/direct activation of the GABA\textsubscript{A} receptors, as is the case with neurosteroids with antidepressant-like activity [85, 86].

Depressive disorders are highly prevalent in diabetic patients. Using a preclinical model of diabetes that was induced by streptozotocin in mice, the effects of the bioflavonoid quercetin (50 and 100 mg/kg, i.p.) were compared with fluoxetine (5 mg/kg, i.p.) and imipramine (15 mg/kg, i.p.) in the forced swim test [115]. Results showed that quercetin significantly reduced depressive-like behavior in diabetic mice, similar to the conventional antidepressants fluoxetine and imipramine. Interestingly, the quercetin-induced reduction of depressive-like behavior was only detected in diabetic mice and not in healthy mice, while fluoxetine and imipramine produced antidepressant-like effects in both

| Flavonoid           | Doses             | Treatment duration | Effects                                                                 | Reference |
|---------------------|-------------------|--------------------|------------------------------------------------------------------------|-----------|
| Apigenin            | 20 and 40 mg/kg   | 21 days            | Increase in BDNF concentrations in the hippocampus in male ICR mice     | [49]      |
| Miquelianin         | 0.6 mg/kg         | 14 days            | Modulation of the hypothalamic-pituitary-adrenal axis by reducing plasma concentration of ACTH and corticosterone in male CD rats | [50]      |
| Isoquercitrin       | 0.6 mg/kg         | 14–56 days         | Modulation of the hypothalamic-pituitary-adrenal axis by reducing plasma concentration of ACTH and corticosterone in male CD rats | [50]      |
| Liquiritin and isoliquiritin | 20 mg/kg | 30 min before sample | Increases in 5-HT and NE concentrations in the hippocampus, hypothalamus, and cortex in mice | [51]      |

BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; MAO-A: monoamine oxidase type A; TrkB: tropomyosin receptor kinase B; 5-HT: serotonin; DA: dopamine; NE: norepinephrine; ACTH: adrenocorticotropic hormone.

Scientifica 7
| Table 3: Effect of flavonoids on depression-like behavior at preclinical research. |
|---|---|---|---|---|---|
| **Model of depression** | **Flavonoid (animal)** | **Dose** | **Treatment duration** | **Effect** | **Reference** |
| Forced swim test | Naringenin (A) | 10 and 20 mg/kg, p.o. | 60 min before test | Antidepressant | [52] |
| 1 | 5, 10, and 20 mg/kg, p.o. | 14 days | Antidepressant | [29] |
| 2 | Hesperidin (H) | 0.1, 0.3, and 1 mg/kg, i.p. | 21 days | Antidepressant | [9] |
| 7,8-Dihydroxyflavone (G) | Icariin (B) | 20 and 40 mg/kg, p.o. | 60 min before test | Antidepressant | [61] |
| Tail suspension test | Naringenin (A) | 10 and 20 mg/kg, p.o. | 60 min before test | Antidepressant | [52] |
| 1 | 5, 10, and 20 mg/kg, p.o. | 14 days | Antidepressant | [29] |
| 2 | Hesperidin (H) | 0.1, 0.3, and 1 mg/kg, i.p. | 21 days | Antidepressant | [9] |
| 7,8-Dihydroxyflavone (G) | Icariin (B) | 20 and 40 mg/kg, p.o. | 60 min before test | Antidepressant | [61] |
| CUMS-sucrose intake | Naringenin (A) | 10 and 20 mg/kg, p.o. | 21 days | Antidepressant | [28] |
| 1 | 5, 10, and 20 mg/kg, p.o. | 21 days | Antidepressant | [28] |
| 2 | Hesperidin (H) | 0.1, 0.3, and 1 mg/kg, i.p. | 21 days | Antidepressant | [9] |
| 7,8-Dihydroxyflavone (G) | Icariin (B) | 20 and 40 mg/kg, p.o. | 60 min before test | Antidepressant | [61] |

1. The antidepressant-like effect is suggested by the reduction in immobility time without significant changes in the general locomotor activity. The antidepressant-like effect is suggested by the increase in sucrose intake. CUMS: chronic unpredictable mild stress. (A) Adult male ICR mice. (B) Male Sprague-Dawley rats. (C) Male C57BL/6J mice. (D) Adult male BALB/c mice. (E) Adult male Wistar rats. (F) Adult male Kunming mice. (G) Adult male C57BL/6 mice. (H) Adult male Swiss mice. (I) Male 21-day streptozotocin-induced diabetic Wistar rats. (J) Female C57BL/6J mice. (K) Mice sex and strain were not identified. (L) Female Swiss mice.
diabetic and healthy mice. In another study, quercetin (50 mg/kg, i.p., for 21 days) also exerted antidepressant-like effects in diabetic rats in the forced swim test. These effects did not involve regulation of the hypothalamic-pituitary-adrenal axis, in which this flavonoid did not produce significant changes in plasma adrenocorticotropic hormone or corticosterone concentrations [54]. These data suggest that quercetin may have a mechanism of action that is different from conventional antidepressants. The antidepressant-like effects of quercetin have been suggested to primarily occur through antioxidative actions and a reduction of proinflammatory cytokine concentrations in the brain [54] that in the long term restore neurochemical function as is the case with conventional antidepressant drugs. Future studies should explore the ability of quercetin to ameliorate symptoms of depression, particularly in diabetic patients.

Finally, studies of the neurobiological bases of depressive disorders and mechanisms of action of antidepressive drugs have shown that reductions of neurotransmitter system activity and BDNF concentrations are associated with depressive symptoms in humans [116] and depression-like behavior in stressor-exposed rats [42]. A reduction of BDNF synthesis has been observed in the hippocampus and cerebral cortex, among other brain structures, in experimental animals. Antidepressant drugs increase BDNF production in both animals and depressed patients [97, 117], suggesting a negative correlation between BDNF concentrations and the severity of depressive symptoms.

Mice that are subjected to CUMS develop symptoms of anhedonia (e.g., a reduction of sucrose preference and consumption) and depressive-like behavior (e.g., increase in immobility time in the forced swim test), and these effects were prevented by oral administration of 5 and 20 mg/kg of the flavonoid chrysin after 28 days of treatment. This antidepressant-like effect of chrysin was accompanied by an increase in BDNF concentrations in the hippocampus and prefrontal cortex and the activation of NGF in mice [10]. Additionally, flavonoid chrysin (5 and 20 mg/kg, p.o., 28 days), similar to antidepressant fluoxetine (10 mg/kg, p.o., 28 days), increases serotonin concentration and reduces the indoleamine-2,3-dioxygenase and caspases 3 and 9 activities in the prefrontal cortex and hippocampus in C57B/6J mice subjected to CUMS, which was associated with the antidepressant-like effect detected in the tail suspension test [118], with the participation of BDNF. Similarly, the administration of 20 and 40 mg/kg of the flavonoid orientin for 21 days also produced antidepressant-like effects in mice that were subjected to CUMS, and this effect was associated with the activation of BDNF and an increase in serotonin and norepinephrine concentration in the hippocampus and cerebral cortex [40]. The administration of 20 and 40 mg/kg of the flavonoid icariin for 35 days also produced antidepressant-like effects in rats that were subjected to CUMS. In that study, control animals presented significant neuronal damage and neuroinflammation in the hippocampus, which were associated with higher oxidative stress. These deleterious effects were reversed by the administration of icariin at doses that reduced depressive-like behavior [42]. These studies suggest that the antioxidant activity and the activation of monoaminergic systems are associated with the production of BDNF by flavonoids [119], ultimately producing antidepressant-like effects in animals. However, this hypothesis requires further exploration.

6. Concluding Remarks

Preclinical data on the antidepressant-like effects of some flavonoids have consistently reported behavioral effects and neurochemical actions in the brain, thus supporting the potential therapeutic application of these natural compounds for the amelioration of depressive symptoms in humans. The data that were reviewed herein implicate BDNF in the antidepressant-like effects of flavonoids. This mechanism of action is relevant because it has been associated with the actions of clinically effective antidepressant drugs [80, 120]. BDNF modulates neurotransmitters and receptor activity and is involved in the activation of serotonergic, noradrenergic, and dopaminergic pathways and neurogenesis in the hippocampus and cerebral cortex, which are implicated in the neurobiology of psychiatric disorders, including depression.

Activation of BDNF and TrkB is produced after administration of conventional antidepressant drugs, such as fluoxetine and citalopram [28, 101, 121], which is associated with the reduction of most of the symptoms of depression [97, 122–124]. Some flavonoids (e.g., 7,8-dihydroxyflavone) also act as TrkB receptor agonists and stimulate neurogenesis in the hippocampus [41]. Such findings may reveal new possibilities for the development of therapeutic alternatives for the treatment of depression, including the administration of subthreshold doses of flavonoids combined with conventional antidepressant drugs. Combined administration of both substances could likely produce antidepressant-like effects with a shorter onset of action through the early stimulation of BDNF production and parallelly modify the neurotransmitter receptor function, which requires further exploration.

Finally, despite the positive findings regarding the antidepressant-like effects of some flavonoids at the preclinical level, potential side effects of long-term consumption need to be investigated, including studies of toxicology and possible pharmacological interactions with other substances, to determine the tolerability and safety of flavonoids in humans. Such studies may eventually demonstrate that some flavonoids are safe alternatives for the treatment of depressive disorders in clinical practice.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors would like to thank Michel Arends for revising and editing the English of this manuscript. León Jesús German-Ponciano and Gilberto Uriel Rosas-Sánchez received fellowships from Consejo Nacional de Ciencia y Tecnología (CONACyT) for postgraduate studies in neuropsychology (Reg. nos. 297560 and 592165, resp.).
References

[1] R. C. Kessler, “The costs of depression,” Psychiatric Clinics of North America, vol. 35, no. 1, pp. 1–14, 2014.

[2] World Health Organization, “Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level: report by the Secretariat,” World Health Organization Geneva, Switzerland, 2011. http://apps.who.int/gb/ebwha/pdf_files/EB130/B130_R8-eng.pdf.

[3] C. J. Harmer, R. S. Duman, and P. J. Cowen, “How do antidepressants work? New perspectives for refining future treatment approaches,” The Lancet Psychiatry, vol. 4, no. 5, pp. 409–418, 2017.

[4] Y. Xing, J. He, J. Hou, F. Lin, J. Tian, and H. Kurihara, “Gender differences in CMS and the effects of antidepressant venlafaxine in rats,” Neurochemistry International, vol. 63, no. 6, pp. 570–575, 2013.

[5] M. Olivares-Nazario, A. Fernández-Guasti, and L. Martínez-Mota, “Age-related changes in the antidepressant-like effect of desipramine and fluoxetine in the rat forced-swim test,” Behavioural Pharmacology, vol. 27, no. 1, pp. 22–28, 2016.

[6] C. López-Rubalcava and E. Estrada-Camarena, “Mexican medicinal plants with anxiolytic or antidepressant activity: Focus on preclinical research,” Journal of Ethnopharmacology, vol. 186, pp. 377–391, 2016.

[7] F. Ferre Navarrete and D. Gimeno Álvarez, “Protocolo diagnóstico y tratamiento de la ansiedad generalizada,” Medicina - Programa de Formación Médica Continuada Acreditado, vol. 10, no. 86, pp. 5846–5850, 2011.

[8] I. Matias, A. S. Buosi, and F. C. A. Gomes, “Functions of flavonoids in the central nervous system: Astrocytes as targets for natural compounds,” Neurochemistry International, vol. 95, pp. 85–91, 2016.

[9] F. Donato, M. G. de Gomes, A. T. R. Goes et al., “Hesperidin exerts antidepressant-like effects in acute and chronic treatments in mice: Possible role of l-arginine-NO-cGMP pathway and BDNF levels,” Brain Research Bulletin, vol. 104, pp. 19–26, 2014.

[10] C. B. Filho, C. R. Jesse, F. Donato et al., “Chronic unpredictable mild stress decreases BDNF and NGF levels and Na+,K+-ATPase activity in the hippocampus and prefrontal cortex of mice: antidepressant effect of chrysin,” Neuroscience, vol. 289, pp. 367–380, 2015.

[11] J. B. Harborne and C. A. Williams, “Advances in flavonoid research since 1992,” Phytochemistry, vol. 55, no. 6, pp. 481–504, 2000.

[12] S. Martínez-Flórez, J. González-Gallego, J. M. Culebras, and M. J. Tuión, “Los flavonoides: propiedades y acciones antioxidantes,” Nutrición Hospitalaria, vol. 17, no. 6, pp. 271–278, 2002.

[13] T. Yan, B. Wu, Z.-Z. Liao et al., “Brain-derived neurotrophic factor signaling mediates the antidepressant-like effect of the total flavonoids of Alpinia oxyphylla fructus in chronic unpredictable mild stress mice,” Phytotherapy Research, vol. 30, no. 9, pp. 1493–1502, 2016.

[14] B. Du, C. Zhang, F. Ren et al., “Antidepressant-like effects of the hydroalcoholic extracts of Hemerocallis citrina and its potential active components,” BMC Complementary and Alternative Medicine, vol. 14, no. 1, p. 326, 2014.

[15] P. Xu, K. Z. Wang, C. Lu et al., “Antidepressant-like effects and cognitive enhancement of the total phenols extract of Hemerocallis citrina Baroni in chronic unpredictable mild stress rats and its related mechanism,” Journal of Ethnopharmacology, vol. 194, pp. 819–826, 2016.

[16] S.-X. Yan, J.-L. Lang, Y.-Y. Song et al., “Studies on antidepressant activity of four flavonoids isolated from Apocynum venetum llini (Apocynaceae) leaf in mice,” Tropical Journal of Pharmaceutical Research, vol. 14, no. 12, pp. 2269–2277, 2015.

[17] M. A. Ebrahimzadeh, S. M. Nabavi, and S. F. Nabavi, “Antidepressant activity of Hibiscus esculentus L,” European Review for Medical and Pharmacological Sciences, vol. 17, no. 19, pp. 2609–2612, 2013.

[18] M. Zheng, Y. Fan, D. Shi, and C. Liu, “Antidepressant-like effect of flavonoids extracted from Apocynum venetum leaves on brain monoamine levels and dopaminergic system,” Journal of Ethnopharmacology, vol. 147, no. 1, pp. 108–113, 2013.

[19] Z. Z. Fan, W. H. Zhao, J. Guo et al., “Antidepressant activities of flavonoids from Glycyrrhiza uralensis and its neurogenesis protective effect in rats,” Acta Pharmaceutica Sinica, vol. 47, no. 12, pp. 1612–1617, 2012.

[20] G. Jia, Z. Weihong, F. Zizhou et al., “Effects of the flavonoids extracted parts on antidepressant activities from Glycyrrhiza uralensis,” Pharmacology and Clinics of Chinese Materia Medica, vol. 6, p. 20, 2012.

[21] M. Herrera-Ruiz, A. Zamilpa, M. González-Cortazar et al., “Antidepressant effect and pharmacological evaluation of standardized extract of flavonoids from Byrsonima crassifolia,” Phytomedicine, vol. 18, no. 14, pp. 1255–1261, 2011.

[22] C. F. Ortmann, G. Z. Réus, Z. M. Ignácio et al., “Enriched flavonoid fraction from coccopia pachystachya tréul leaves exerts antidepressant-like behavior and protects brain against oxidative stress in rats subjected to chronic mild stress,” Neurotoxicity Research, vol. 29, no. 4, pp. 469–483, 2016.

[23] J. Cassani, O. A. Ferreyra-Cruz, A. M. Dorantes-Barrón, R. M. Viguera Villasénor, D. Arrieta-Baez, and R. Estrada-Reyes, “Antidepressant-like and toxicological effects of a standardized aqueous extract of Chrysactinia mexicana A. Gray (Asteraceae) in mice,” Journal of Ethnopharmacology, vol. 171, pp. 295–306, 2015.

[24] S. Park, Y. Sim, P. Han, J. Lee, and H. Suh, “Antidepressant-like effect of kaempferol and quercitirin, isolated from Opuntia ficus-indica var.Saboten,” Experimental Neurobiology, vol. 19, no. 1, p. 30, 2010.

[25] P. B. Shewale, R. A. Patil, and Y. A. Hiray, “Antidepressant-like activity of anthocyanidins from Hibiscus rosa-sinensis flowers in tail suspension test and forced swim test,” Indian Journal of Pharmacology, vol. 44, no. 4, pp. 454–457, 2012.

[26] S. Batra and S. Kumar, “Antidepressant activity evaluation of Actaea spicata L. Roots,” Journal of Fundamental Pharmaceutical Chemical Research, vol. 2, no. 1, pp. 1–6, 2014.

[27] B. K. Vazhayil, S. S. Rajagopal, T. Thangavelu, G. Swaminathan, and R. Rajagounder, “Neuroprotective effect of Clerodendrum serratum Linn. leaves extract against acute restraint stress-induced depressive-like behavioral symptoms in adult mice,” Indian Journal of Pharmacology, vol. 49, no. 1, pp. 34–41, 2017.

[28] L.-T. Yi, B.-B. Liu, J. Li et al., “BDNF signaling is necessary for the antidepressant-like effect of naringenin,” Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 48, pp. 135–141, 2014.

[29] L.-T. Yi, J. Li, H.-C. Li et al., “Antidepressant-like behavioral, neurochemical and neuroendocrine effects of naringenin in the mouse repeated tail suspension test,” Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 39, no. 1, pp. 175–181, 2012.
V. N. Thakare, M. K. Aswar, Y. P. Kulkani, R. R. Patil, and Y. Liu, N. Lan, J. Ren et al., “Orientin improves depression-

B.Liu,C.Xu,X.Wuetal.,”Icariinexertsanantidepressanteffect

Q.-Q. Lv, W.-J. Wu, X.-L. Guo et al., “Antidepressant activity of

Z. Xiong, B. Jiang, P.-F. Wu et al., “Antidepressant effects

L. Zhen, J. Zhu, X. Zhao et al., “The antidepressant-like effect of

B. Lee, B. Sur, J. Park et al., “Chronic administration of

M. S. Antunes, C. R. Jesse, J. R. Ruff et al., “Hesperidin reverses
cognitive and depressive disturbances induced by olfactory
bullectomy in mice by modulating hippocampal neurotrophins and
cytokine levels and acetylcholinesterase activity,” European
Journal of Pharmacology, vol. 789, pp. 411–420, 2016.

Q.-Q. Lv, W.-J. Wu, X.-L. Guo et al., “Antidepressant activity of
astilbin: Involvement of monoaminergic neurotransmitters and
BDNF signal pathway,” Biological & Pharmaceutical Bulletin,
vol. 37, no. 6, pp. 987–995, 2014.

B. Lee, B. Sur, J. Park et al., “Chronic administration of
baicalein decreases depression-like behavior induced by
repeated restraint stress in rats,” Korean Journal of Physiology
& Pharmacology, vol. 17, no. 5, pp. 393–403, 2013.

Z. Xiong, B. Jiang, P.-F. Wu et al., “Antidepressant effects of
a plant-derived flavonoid baicalein involving extracellular
signal-regulated kinases cascade,” Biological & Pharmaceutical
Bulletin, vol. 34, no. 2, pp. 253–259, 2011.

C. B. Filho, C. R. Jesse, F. Donato et al., “Chrysin promotes atten-
uation of depressive-like behavior and hippocampal dysfunc-
tion resulting from olfactory bullectomy in mice,” Chemico-
Biological Interactions, vol. 260, pp. 154–162, 2016.

L. Zhen, J. Zhu, X. Zhao et al., “The antidepressant-like effect of
fisetin involves the serotonergic and noradrenergic system,”
Behavioural Brain Research, vol. 228, no. 2, pp. 359–366, 2012.

Y. Wang, B. Wang, J. Lu et al., “Fisetin provides antidepressant
effects by activating the tropomyosin receptor kinase B signal
pathway in mice,” Journal of Neurochemistry, vol. 143, no. 5, pp.
561–568, 2017.

Y. Liu, N. Lan, J. Ren et al., “Orientin improves depression-
like behavior and BDNF in chronic stressed mice,” Molecular
Nutrition & Food Research, vol. 59, no. 6, pp. 1130–1142, 2015.

L.-M. Zhang, H.-L. Wang, N. Zhao, H.-X. Chen, Y.-F. Li, and Y.-Z.
Zhang, “Involvement of nitric oxide (NO) signaling pathway in
the antidepressant action of the flavonoids extracted from
Xiaobuxin-Tang,” Neuroscience Letters, vol. 575, pp. 31–36, 2014.

B. Liu, C. Xu, X. Wu et al., “Icariin exerts an antidepressant effect in
an unpredictable chronic mild stress model of depression in rats
and is associated with the regulation of hippocampal
neuroinflammation,” Neuroscience, vol. 294, pp. 193–205, 2015.

Z. Ren, P. Yan, L. Zhu et al., “Dihydromyricetin exerts a rapid
antidepressant-like effect in association with enhancement of
BDNF expression and inhibition of neuroinflammation,”
Psychopharmacology, vol. 230, no. 1, pp. 233–244, 2018.

V. N. Thakare, M. K. Aswar, Y. P. Kulkani, R. R. Patil, and
B. M. Patel, “Silymarin ameliorates experimentally induced
depressive like behavior in rats: Involvement of hippocampal
BDNF signaling, inflammatory cytokines and oxidative stress
response,” Physiology Behavior, vol. 179, pp. 401–410, 2017.

E. Meyer, M. A. Mori, A. C. Campos et al., “Myricitin induces
antidepressant-like effects and facilitates adult neurogenesis
in mice,” Behavioural Brain Research, vol. 316, pp. 59–65, 2017.

Z. Ma, G. Wang, L. Cui, and Q. Wang, “Myricetin attenuates
depressant-like behavior in mice subjected to repeated restraint
stress,” International Journal of Molecular Sciences, vol. 16, no.
12, pp. 28377–28385, 2015.

A. Sawamoto, S. Okuyama, K. Yamamoto et al., “3,5,6,7,8,31-
Heptamethoxyflavone, a citrus flavonoid, Ameliorates corti-
costerone-induced depression-like behavior and restores brain-
derived neurotrophic factor expression, neurogenesis, and
neuropasticity in the hippocampus,” Molecules, vol. 21, no. 4,
article no. 541, 2016.

A. Sawamoto, S. Okuyama, Y. Amakura et al., “3,5,6,7,8,31-
Heptamethoxyflavone ameliorates depressive-like behavior and
hippocampal neurochemical changes in chronic unpredictable
mild stressed mice by regulating the brain-derived neurotrophic
factor: requirement for erk activation,” International Journal of Molecular Sciences, vol. 18, no. 10, p. 2133, 2017.

L. Weng, X. Guo, Y. Li, X. Yang, and Y. Han, “Apigenin reverses
depression-like behavior induced by chronic corticosterone
treatment in mice,” European Journal of Pharmacology, vol. 774,
pp. 50–54, 2016.

V. Butterweck, M. Hegger, and H. Winterhoff, “Flavonoids of St.
John’s Wort reduce HPA axis function in the rat,” Planta Medica,
vol. 70, no. 10, pp. 1008–1011, 2004.

W. Wang, X. Hu, Z. Zhao et al., “Antidepressant-like effects of
liquiritin and isoliquiritin from Glycyrrhiza uralensis in the
forced swimming test and tail suspension test in mice,” Progress
in Neuro-Psychopharmacology & Biological Psychiatry, vol. 32,
no. 5, pp. 1179–1184, 2008.

L.-T. Yi, C.-F. Li, X. Zhan et al., “Involvement of monoamine-
ergic system in the antidepressant-like effect of the flavonoid
naringenin in mice,” Progress in Neuro-Psychopharmacology &
Biological Psychiatry, vol. 34, no. 7, pp. 1223–1228, 2010.

Ö. D. Can, Ü. Demir Özkay, and U. I. Uçel, “Anti-depressant-
like effect of vيتixin in BALB/c mice and evidence for the
involvement of monoaminergic mechanisms,” European Journal
of Pharmacology, vol. 699, no. 1-3, pp. 250–257, 2013.

E. A. Demir, H. S. Gengerlioglu, and M. Oz, “Antidepressant-
like effects of quercetin in diabetic rats are independent of
hypothalamic-pituitary-adrenal axis,” Acta Neuropsychiatrica,
vol. 28, no. 1, pp. 23–30, 2016.

S. Rinwa and A. Kumar, “Quercetin suppress microglial neu-
roinflammatory response and induce antidepressant-like effect
in olfactory bullectomized rats,” Neuroscience, vol. 255, pp.
86–98, 2013.

I. Holzmann, L. M. Da Silva, J. A. Corrêa Da Silva, V. M. B.
Steimbach, and M. M. De Souza, “Antidepressant-like effect
of quercetin in bullectomized mice and involvement of the
antioxidant defenses, and the glutamatergic and oxidonitrergic
pathways,” Pharmacology Biochemistry & Behavior, vol. 136,
pp. 55–63, 2015.

M. González-Cortazar, A. M. Maldonado-Abarca, E. Jiménez-
Ferrer et al., “Issosakuranetin-5-O-rutinoside: A New Flavanone
with Antidepressant Activity Isolated from SalviaelegansVahl,”
Planta Medica, vol. 789, pp. 411–420, 2016.

M. Kwatra, A. Jangra, M. Mishra et al., “Naringin and
sertraline ameliorate doxorubicin-induced behavioral deficits
in mice,” European Journal of Pharmacology, vol. 774,
pp. 50–54, 2016.
through modulation of serotonin level and mitochondrial complex protection pathway in rat hippocampus,” *Neurochemical Research*, vol. 41, no. 9, pp. 2352–2366, 2016.

59. L.-T. Yi, J.-M. Li, Y.-C. Li, Y. Pan, Q. Xu, and L.-D. Kong, “Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin,” *Life Sciences*, vol. 82, no. 13-14, pp. 741–751, 2008.

60. M.-W. Zhang, S.-F. Zhang, Z.-H. Li, and F. Han, “7,8-Dihydroxyflavone reverses the depressive symptoms in mouse chronic mild stress,” *Neuroscience Letters*, vol. 635, pp. 33–38, 2016.

61. K. Wei, Y. Xu, Z. Zhao et al., “Icarin alters the expression of glucocorticoid receptor, FKB5 and SGK1 in rat brains following exposure to chronic mild stress,” *International Journal of Molecular Medicine*, vol. 38, no. 1, pp. 337–344, 2016.

62. S. P. Fernández, C. Wasowski, L. M. Loscalzo et al., “Central nervous system depressant action of flavonoid glycosides,” *European Journal of Pharmacology*, vol. 539, no. 3, pp. 168–176, 2006.

63. A. C. Paladini, M. Marder, H. Viola, C. Wolfman, C. Wasowski, and J. H. Medina, “Flavanoids and the central nervous system: From forgotten factors to potent anxiolytic compounds,” *Journal of Pharmacy and Pharmacology*, vol. 51, no. 5, pp. 519–526, 1999.

64. E. Middleton Jr., C. Kandaswami, and T. C. Theoharides, “The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer,” *Pharmacological Reviews*, vol. 52, no. 4, pp. 673–751, 2000.

65. S. F. Nabavi, N. Braidy, S. Habtemariam et al., “Neuroprotective effects of chrysin: from chemistry to medicine,” *Neurochemistry International*, vol. 90, pp. 224–231, 2015.

66. M. Bakhtiari, Y. Panahi, J. Ameli, and B. Darvishi, “Protective effects of flavonoids against Alzheimer’s disease-related neural dysfunctions,” *Biomedicine & Pharmacotherapy*, vol. 93, pp. 218–229, 2017.

67. M. Ebadi, *Pharmacodynamic Basis of Herbal Medicine*, CRC Press, Florida, FL, USA, 2001.

68. J.-G. Berrin, W. R. McLauchlan, P. Needs et al., “Functional expression of human liver cytosolic β-glucosidase in Pichia pastoris: Insights into its role in the metabolism of dietary glycosides,” *European Journal of Biochemistry*, vol. 269, no. 1, pp. 249–258, 2002.

69. K. Németh, G. W. Plumb, J.-G. Berrin et al., “Deglycosylation by small intestinal epithelial cell β-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans,” *European Journal of Nutrition*, vol. 42, no.1, pp. 29–42, 2003.

70. C. Manach, A. Scalbert, C. Morand, C. Rémyé, and L. Jiménez, “Polyphenols: food sources and bioavailability,” *American Journal of Clinical Nutrition*, vol. 79, no. 5, pp. 727–747, 2004.

71. A. Roobhaksh, H. Parhiz, F. Soltani, R. Rezaee, and M. Iranshahi, “Neuropharmacological properties and pharmacokinetics of the citrus flavonoids hesperidin and hesperetin - A mini-review,” *Life Sciences*, vol. 113, no.1-2, pp. 1–6, 2014.

72. U. K. Walle, A. Galijatovic, and T. Walle, “Transport of the flavonoid chrysin and its conjugated metabolites by the human intestinal cell line Caco-2,” *Biochemical Pharmacology*, vol. 58, no. 3, pp. 431–438, 1999.

73. A. G. de Boer and P. J. Gaillard, “Drug targeting to the brain,” *Annual Review of Pharmacology and Toxicology*, vol. 47, no. 1, pp. 323–355, 2007.

74. I. Méndez-David, L. Tritschler, Z. El Ali et al., “Nrf2-signaling and BDNF: A new target for the antidepressant-like activity of chronic fluoxetine treatment in a mouse model of anxiety/depression,” *Neuroscience Letters*, vol. 597, pp. 121–126, 2015.

75. R. Ghosh, R. Gupta, M. S. Bhatia, A. K. Tripathi, and L. K. Gupta, “Comparison of efficacy, safety and brain derived neurotrophic factor (BDNF) levels in patients of major depressive disorder, treated with fluoxetine and desvenlafaxine,” *Asian Journal of Psychiatry*, vol. 18, pp. 37–41, 2015.

76. H. H. Stassen, J. Angst, and A. Delini-Stula, “Delayed onset of action of antidepressant drugs. Survey of recent results,” *European Psychiatry*, vol. 12, no. 4, pp. 166–176, 1997.

77. J. Sarris and D. J. Kavanagh, “Kava and St. John’s wort: Current evidence for use in mood and anxiety disorders,” *The Journal of Alternative and Complementary Medicine*, vol. 15, no. 8, pp. 827–836, 2009.

78. Q. Wang, M. A. Timberlake, K. Prall, and Y. Dwivedi, “The recent progress in animal models of depression,” *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 77, pp. 99–109, 2017.

79. H. M. Abelaiba, G. Z. Réus, and J. Quevedo, “Animal models as tools to study the pathophysiology of depression,” *Revista Brasileira de Psiquiatria*, vol. 35, no. 2, pp. S112–S120, 2013.

80. C. Zhou, J. Zhong, B. Zou et al., “Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression,” *PLoS ONE*, vol. 12, no. 2, Article ID e0172270, 2017.

81. H. Park, S. Yoon, J. Choi et al., “The antidepressant effects of Cirsium japonicum in ICR mice,” *Yakkho Hooji*, vol. 50, no. 6, pp. 429–435, 2006.

82. A. Abdelhalim, N. Karim, M. Chebib et al., “Antidepressant, anxiolytic and antinociceptive activities of constituents from rosmarinus officinalis,” *Journal of Pharmacy & Pharmaceutical Sciences*, vol. 18, no. 4, pp. 448–459, 2015.

83. M. Lin, H. Li, Y. Zhao et al., “Ergosterol 2-naphthoate, an ergosterol derivative, exhibits antidepressant effects mediated by the modification of GABAergic and glutamatergic systems,” *Molecules*, vol. 22, no. 4, article no. 565, 2017.

84. R. T. Khisti, C. T. Chopde, and S. P. Jain, “Antidepressant-like effect of the neurosteroid 3α-hydroxy-5α-pregn-20-one in mice forced swim test,” *Pharmacology Biochemistry & Behavior*, vol. 67, no. 1, pp. 137–143, 2000.

85. J. F. Rodríguez-Landa, C. M. Contreras, B. Bernal-Morales, A. G. Gutiérrez-Garcia, and M. Saavedra, “Allopregnanolone reduces immobility in the forced swimming test and increases the firing rate of lateral septal neurons through actions on the GABA_A receptor in the rat,” *Journal of Psychopharmacology*, vol. 21, no. 1, pp. 76–84, 2007.

86. J. F. Rodríguez-Landa, C. M. Contreras, and R. I. García-Rios, “Allopregnanolone microinjected into the lateral septum or dorsal hippocampus reduces immobility in the forced swim test: Participation of the GABA_A receptor,” *Behavioural Pharmacology*, vol. 20, no. 7, pp. 614–622, 2009.

87. D. G. Machado, L. E. B. Bettio, M. P. Cunha et al., “Anti-depressant-like activity of rutin isolated from the ethanolic extract from Schinus molle L.” in mice: Evidence for the involvement of the serotonergic and noradrenergic systems,” *European Journal of Pharmacology*, vol. 587, no. 1-3, pp. 163–168, 2008.

88. A. Paulke, M. Nöldner, M. Schubert-Zsilavecz, and M. Würlichs, “St. John’s wort flavonoids and their metabolites show evidence for use in mood and anxiety disorders,” *European Journal of Pharmacology*, vol. 587, no. 1-3, pp. 163–168, 2008.
antidepressant activity and accumulate in brain after multiple oral doses,” *Die Pharmazie*, vol. 63, no. 4, pp. 296–302, 2008.

[89] S. Yoshino, A. Hara, H. Sakakibara et al., “Effect of quercetin and glucuronide metabolites on the monoamine oxidase-A reaction in mouse brain mitochondria,” *Nutrition Journal*, vol. 27, no. 7-8, pp. 847–852, 2012.

[90] L. An, J. Li, S.-T. Yu et al., “Effects of the total flavonoid extract of Xiaobuxin-Tang on depression-like behavior induced by lipopolysaccharide and proinflammatory cytokine levels in mice,” *Journal of Ethnopharmacology*, vol. 163, pp. 83–87, 2015.

[91] S.-H. Lin, M.-L. Chou, W.-C. Chen et al., “A medicinal herb, Melissa officinalis L. ameliorates depressive-like behavior of rats in the forced swimming test via regulating the serotonergic neurotransmitter,” *Journal of Ethnopharmacology*, vol. 175, article no. 9741, pp. 266–272, 2015.

[92] A. E. Taiwo, F. B. Leite, G. M. Lucena et al., “Anxiolytic and antidepressant-like effects of Melissa officinalis (lemon balm) extract in rats: Influence of administration and gender,” *Indian Journal of Pharmacology*, vol. 44, no. 2, pp. 189–192, 2012.

[93] V. López, S. Martín, M. P. Gómez-Serranillos, M. E. Carretero, A. K. Jäger, and M. I. Calvo, “Neuroprotective and neurological properties of Melissa officinalis,” *Neurochemical Research*, vol. 34, no. 11, pp. 1955–1961, 2009.

[94] G. Rubio, L. San, F. López-Muñoz, and P. García-García, “Tratamiento de combinación con reboxetina en pacientes con depresión mayor no respondedores o con respuesta parcial a inhibidores selectivos de la recaptación de serotonina,” *Actas Españolas de Psiquiatría*, vol. 31, no. 6, pp. 315–324, 2003.

[95] S. P. Patil, C. Liu, J. Alban, N. Yang, and X. Li, “Glycyrrhiza uralensis flavonoids inhibit brain microglial cell TNF-α secretion, p-IκB expression, and increase brain-derived neurotrophic factor (BDNF) secretion,” *Journal of Traditional Chinese Medicine Sciences*, vol. 1, no. 1, pp. 28–37, 2014.

[96] L. C. Souza, M. S. Antunes, C. B. Filho et al., “Flavonoid Chrysins prevents age-related cognitive decline via attenuation of oxidative stress and modulation of BDNF levels in aged mouse brain,” *Pharmacology Biochemistry & Behavior*, vol. 134, pp. 22–30, 2015.

[97] E. Castrén and M. Kojima, “Brain-derived neurotrophic factor in mood disorders and antidepressant treatments,” *Neurobiology of Disease*, vol. 97, pp. 119–126, 2017.

[98] G. Y. Su, J. Y. Yang, F. Wang et al., “Antidepressant-like effects of Xiaochaihu tang in a rat model of chronic unpredictable mild stress,” *Journal of Ethnopharmacology*, vol. 152, no. 1, pp. 217–226, 2014.

[99] S. Ostadhadi, M. Ahangari, V. Nikoui et al., “Pharmacological evidence for the involvement of the NMDA receptor and nitric oxide pathway in the antidepressant-like effect of lamotrigine in the mouse forced swimming test,” *Biomedicine & Pharmacotherapy*, vol. 82, pp. 713–721, 2016.

[100] V. Butterweck, S. Nishibe, T. Sasaki, and M. Uchida, “Antidepressant effects of apocynum venetum leaves in a forced swimming test,” *Biological & Pharmaceutical Bulletin*, vol. 24, no. 7, pp. 848–851, 2001.

[101] J.-C. Zhang, J. Wu, Y. Fujita et al., “Antidepressant effects of TinkB ligands on depression-like behavior and dendritic changes in mice after inflammation,” *International Journal of Neuropsychopharmacology*, vol. 18, no. 4, 2015.

[102] M. E. Breuer, L. Groenink, R. S. Oosting et al., “Antidepressant effects of pramipexole, a dopamine D3/D2 receptor agonist, and 7-OH-DPAT, a dopamine D3 receptor agonist, in olfactory bulbectomized rats,” *European Journal of Pharmacology*, vol. 616, no. 1-3, pp. 134–140, 2009.

[103] Y. Li, Z. R. Zhu, B. C. Ou et al., “Dopamine D2/D3 but not dopamine D1 receptors are involved in the rapid antidepressant-like effects of ketamine in the forced swim test,” *Behavioural Brain Research*, vol. 279, pp. 100–105, 2015.

[104] J. Song, X. Hou, X. Hu et al., “Not only serotonergic system, but also dopaminergic system involved in albiflorin against chronic unpredictable mild stress-induced depression-like behavior in rats,” *Chemico-Biological Interactions*, vol. 242, pp. 211–217, 2015.

[105] P. Willner, J. Scheel-Krüger, and C. Belzung, “The neurobiology of depression and antidepressant action,” *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 10, pp. 2331–2371, 2013.

[106] L. C. Souza, M. G. de Gomes, A. T. R. Goes et al., “Evidence for the involvement of the serotonergic 5-HT1A receptors in the antidepressant-like effect caused by hesperidin in mice,” *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 40, no. 1, pp. 103–109, 2013.

[107] W. Zhu, S. Ma, R. Qu, D. Kang, and Y. Liu, “Antidepressant effect of baikalin extracted from the root of Scutellaria baicalensis in mice and rats,” *Pharmacological Bulletin*, vol. 44, no. 7, pp. 503–510, 2008.

[108] M. J. Detke, M. Rickels, and I. Lucki, “Active behaviors in the rat forced swimming test differentially produced by serotoninergic and noradrenergic antidepressants,” *Psychopharmacology*, vol. 121, no. 1, pp. 66–72, 1995.

[109] L. T. Yi, H. L. Xu, J. Feng, X. Zhan, L. P. Zhou, and C. C. Cui, “Involvement of monoaminergic systems in the antidepressant like effect of nobiletin,” *Physiology Behavior*, vol. 102, no. 1, p. 1, 2011.

[110] R. Lozano-Hernández, J. F. Rodríguez-Landa, J. D. Hernández-Figueroa, M. Saavedra, F. R. Ramos-Morales, and J. S. Cruz-Sánchez, “Antidepressant-like effects of two commercially available products of Hypericum perforatum in the forced swim test: A long-term study,” *Journal of Medicinal Plants Research*, vol. 4, no. 2, pp. 131–137, 2010.

[111] J. F. Rodríguez-Landa, J. Cueto-Escobedo, J. D. Aguirre-Chiñas, and M. O. Pérez-Vázquez, “A commercially available product of Hypericum perforatum acts on GABAA receptor to produces anxiolytic-like, but not antidepressant-like effects in Wistar rats,” in *Hypericum: Botanical Sources, Medical Properties, and Health Effects*, H. R. Davis, Ed., Davis, Nova Publishers, New York, NY, USA, 2015.

[112] E. A. Apaydin, A. R. Maher, R. Shamman et al., “A systematic review of St. John’s wort for major depressive disorder,” *Systematic Reviews*, vol. 5, no. 1, article no. 148, 2016.

[113] J. F. Rodríguez-Landa and C. M. Contreras, “A review of clinical and experimental observations about antidepressant actions and side effects produced by Hypericum perforatum extracts,” *Phytomedicine*, vol. 10, no. 8, pp. 688–699, 2003.

[114] N. Karim, I. Khan, N. Ahmad, M. N. Umar, and N. Gavande, “Antidepressant, anticonvulsant and antinociceptive effects of 3'-methoxy-6-methylflavone and 3'-hydroxy-6-methylflavone may involve GABAergic mechanisms,” *Pharmacological Reports*, vol. 69, no. 5, pp. 1014–1020, 2017.

[115] M. Anjanyelulu, K. Chopra, and I. Kaur, “Antidepressant Activity of Quercetin, A Bioflavonoid, in Streptozocin-Induced Diabetic Mice,” *Journal of Medicinal Food*, vol. 6, no. 4, pp. 391–395, 2003.

[116] Q.-Q. Mao, Z. Huang, X.-M. Zhong, Y.-F. Xian, and S.-P. Ip, “Brain-derived neurotrophic factor signalling mediates the
antidepressant-like effect of piperine in chronically stressed mice,” *Behavioural Brain Research*, vol. 261, pp. 140–145, 2014.

[117] A. D. Başterzi, K. Yazıcı, E. Aslan et al., “Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients,” *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 33, no. 2, pp. 281–285, 2009.

[118] C. B. Filho, C. R. Jesse, F. Donato et al., “Neurochemical factors associated with the antidepressant-like effect of flavonoid chrysin in chronically stressed mice,” *European Journal of Pharmacology*, vol. 791, pp. 284–296, 2016.

[119] S. Kumar, A. Mishra, and A. K. Pandey, “Antioxidant mediated protective effect of *Parthenium hysterophorus* against oxidative damage using in *vitro* models,” *BMC Complementary and Alternative Medicine*, vol. 13, article 120, 2013.

[120] G. Li, P. Jing, Z. Liu et al., “Beneficial effect of fluoxetine treatment against psychological stress is mediated by increasing BDNF expression in selected brain areas,” *Oncotarget*, vol. 8, no. 41, pp. 69527–69537, 2017.

[121] T. Rantamäki, P. Hendolin, A. Kankaanpää et al., “Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-Cγ signaling pathways in mouse brain,” *Neuropsychopharmacology*, vol. 32, no. 10, pp. 2152–2162, 2007.

[122] K. Hashimoto, “Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions,” *Psychiatry and Clinical Neurosciences*, vol. 64, no. 4, pp. 341–357, 2010.

[123] K. Hashimoto, “Role of the mTOR signaling pathway in the rapid antidepressant action of ketamine,” *Expert Review of Neurotherapeutics*, vol. 11, no. 1, pp. 33–36, 2011.

[124] R. S. Duman and G. K. Aghajanian, “Synaptic dysfunction in depression: potential therapeutic targets,” *Science*, vol. 338, no. 6103, pp. 68–72, 2012.