Antidepressant-like Effect of Flavonoids

Subjects: Psychology, Experimental

Contributor: León Jesús German-Ponciano, Gilberto Uriel Rosas-Sánchez, Jonathan Cueto-Escobedo, Rafael Fernández-Demeneghi, Gabriel Guillén-Ruiz, César Soria-Fregozo, Emma Virginia Herrera-Huerta, Juan Francisco Rodríguez-Landa

Depressive disorders are among the most disabling diseases experienced around the world. The search for new pharmacological alternatives to treat depression is a global priority. In preclinical research, molecules obtained from plants, such as flavonoids, have shown promising antidepressant-like properties through several mechanisms of action that have not been fully elucidated, including crossing of the blood brain barrier (BBB).

Keywords: depression ; flavonoid ; serotonin ; BDNF ; polyphenol

1. Searching for Alternatives to Antidepressant Drugs

Despite the great advances in pharmacological research on antidepressant drugs, even during the latency period with new treatments patients continue suffering from depressive symptoms and some even drop out of treatment [1]. In addition, some patients have an increased risk of suicide during the first week of pharmacological treatment [2]. These characteristics drive the search for new active compounds with faster effects such as probiotics [3] or ketamine, whose effects are related to rapid molecular neuroplasticity; however, their clinical use is unfortunately limited by its poor safety and development of pharmacological tolerability [4][5]. As a consequence, the identification, evaluation, and development of new antidepressant substances with improved efficacy and apparently fewer side effects has become the main objective of numerous studies [6].

In this sense, the study of phytochemical compounds, such as flavonoids, is a growing field in neuropharmacology research [7][8], especially due to their impact on the central nervous system (CNS), including their potential antidepressant-like effects [6][9][10].

2. Pharmacokinetics of Flavonoids and Their Entry into the CNS

Most flavonoids are present in food in their O-glycoside form, with glucose being the most common β-linked residue, but glucoramnose, galactose, arabinose, and rhamnose are also present [11]. Once they are ingested and before entering the general circulation, these glycosides can undergo deglycosylation (hydrolysis), which takes place in either the small or large intestines depending on the type of sugar [12]. This process is carried out by two β-glucosidase enzymes: lactase-phlorizin hydrolase, which hydrolyzes lactose, glucose, and galactose, and cytosolic β-glycosidase, which has specificity dependent on the aglycone moiety [13]. The next step is the passive diffusion of the flavonoid aglycones through epithelial cells [14]. In this sense, isoflavones are the most efficiently absorbed, while flavanols and flavanones are intermediately absorbed, and proanthocyanins and anthocyanins are poorly absorbed [15].

After absorption, flavonoids are transported to the liver for further metabolism through different conjugation reactions such as O-methylation, sulfation, and glucuronidation. Due to flavonoids having a high conjugation capacity, their concentration in plasma is generally low [11]. These metabolites can also undergo oxidative metabolism mediated by cytochrome P450 enzymes. Likewise, metabolism can be carried out through bacteria in the colon, which hydrolyzes the parent, and in the upper part of the intestine unmetabolized flavonoids as well as their glucuronides and sulfates can be found. Some research has reported that conjugation reactions with glucuronic acid and/or sulfate are the most common for flavonoids. Finally, because of the metabolism of flavonoids, more hydrophilic compounds are obtained and hence eliminated through different routes. In the case of flavonoids, elimination in the bile is quantitatively the most important elimination route [12].

On the other hand, despite some research showing that diets rich in flavonoids have various therapeutic effects both at the systemic level and in the CNS [16][17][18][19], most studies have reported the presence of these compounds and their metabolites at the peripheral level, but little has been explored with respect to their bioavailability in the brain and the mechanisms that facilitate their transport through the blood–brain barrier (BBB) [20].

Epicatechin (a flavanol found mostly in cocoa and green tea) and its methylated form (3′-O-methyl epicatechin) were found in the brains of rats after (1, 5, and 10 days) its oral administration (100 mg/kg body weight/d) [21]. The capacity of epicatechin and its metabolite to cross the BBB in an in vitro model hCMEC/D3c cell culture has also been evaluated. Both were found to cross the BBB in a time-dependent manner (at 3 and 18 h), although with higher efficiency for the methylated metabolite. This suggests that the transport process involved is likely passive diffusion, since methylated molecules are more lipophilic than unconjugated epicatechin and, therefore, more easily cross the BBB [22].

Similarly, quercetin and its metabolite (3-O-glucuronyl-quercetin; 50 mg/kg body wt; p.o.) were found in rat brain tissue in a capillary endothelial cell line [23]; its transportation through the BBB was also evaluated. In this sense, it was found that quercetin and its glucuronidated form crossed the BBB (a model cell line hCMEC/D3), increasing its concentration as time passed (over 1, 3, and 18 h). However, its metabolite showed a faster rate [22].

Interestingly, in the case of anthocyanins, these compounds have only been identified intact or glycosylated (unconjugated) in the CNS [24][25]. Three anthocyanins were evaluated: delphinidin-3-O-glucoside (Dp-3-gl), cyanidin-3-O-glucoside (Cy-3-gl), and malvidin-3-O-glucoside (Mv-3-gl), and all crossed hCMEC/D3 cells in a time-dependent manner (over 1, 3, and 18 h) but showed different efficiencies associated with their hydrophilicity. Dp-3-gl is the most hydrophilic and, therefore, least efficient of the three derivatives, which suggests the influence in which the polarity of anthocyanins plays in their transport through the BBB [22]. In addition, the neuroprotective effects of flavonoids could possibly be mainly exerted by their conjugated metabolites, considering that a mixture of different conjugated quercetin metabolites was shown to exert more effective antihypertensive effects than the isolated molecule [26].

3. Participation of Serotonergic System in the Antidepressant-like Effect of Flavonoids

Diverse preclinical studies have evaluated the effect of flavonoids in promoting the development of new alternatives for treating depression [6]. In this sense, the antidepressant-like effect produced by flavonoids has been demonstrated using animal models of depression such as the FST, TST, or sucrose water consumption test [27], among others. These effects are associated with the modulation of several neurotransmission systems such as noradrenergic, dopaminergic, and serotonergic [28][29]. **Table 1** summarizes the findings regarding the antidepressant potential of some flavonoids that exert their action through the serotonergic system, which has been extensively related to the etiology of depression and the mechanism of action of antidepressant drugs [29][30][31].

Table 1. Flavonoids with antidepressant-like effects and their action on the serotonergic system.

Flavonoid	Experimental Subjects	Treatment	Behavioral Effect	Effect on Serotonergic System	Reference
Astilbin (taxifolin-3-O-rhamnoside)	Adult male C57BL/6J mice	10, 20, and 40 mg/kg (i.p.) for 21 days	↓ TTI in FST and TST ↑ Sucrose intake	↑ 5-HT in frontal cortex	[32]
Hesperidin (3,5,7-trihydroxyflavanone-7-rhamnoglucoside)	Male adult Swiss mice	0.1, 0.3, and 1 mg/kg (i.p.) S.D. 30 min before behavioral test	↓ TTI in FST and TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevents antidepressant-like effect	[33]
	Adult male Wistar rats with hyperglycemia induced by streptozotocin	25, 50, and 100 mg/kg (p.o.) for 21 days	↓ TTI in FST	↑ Brain levels of 5-HT	[34]
	Male Swiss Albino mice	1 mg/kg (i.p.) for 14 days	↓ TTI in FST and TST	↑ 5-HT in HP and cerebral cortex	[35]
	Old male Sprague-Dawley rats	20, 50, and 100 mg/kg (i.p.) for 14 days	↑ Sucrose intake ↓ TTI in FST	↑ 5-HT in HP, PFC, and amygdala	[36]

Flavonoid	Experimental Subjects	Treatment	Behavioral Effect	Effect on Serotonergic System	Reference
Rutin (quercetin-3-*O*-rhamnosylglucoside)	Male Swiss mice	0.01, 0.1, 0.3, 1, 3, and 10 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in FST	Pretreatment with pCPA (100 mg/kg, i.p.) prevents antidepressant-like effect	[37]
	Five weeks old male Sprague Dawley rats	225 mg/kg (p.o.) for 28 days	↓ TTI ↑ Swimming time in FST	↑ 5-HT in frontal cortex, HP, striatum, and amygdala	[38]
Icariin (7-(β-D-Glucopyranosyloxy)-5-hydroxy-4′-methoxy-8-(3-methylbut-2-en-1-yl)-3-(α-L-rhamnopyranosyloxy) flavone)	Adult male Wistar rats	30 and 60 mg/kg (p.o.) for 5 weeks	↑ Sucrose intake	↑ 5-HT_{1A} mRNA levels in HP and frontal cortex	[39]
Orientin (luteolin-8-C-glucoside)	Adult male Kunming mice	20 and 40 mg/kg (p.o.) 3 weeks	↑ Sucrose intake	↑ 5-HT in HP and PFC	[40]
Hyperoside (quercetin 3-galactoside)	Male Albino Swiss mice	3.75 mg/kg (i.p.) 60 min before the behavioral test	↓ TTI in FST and TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of hyperoside	[41]
Quercetin	Male Swiss Albino mice	25 mg/kg (p.o.) for 4 weeks	↓ TTI in FST and TST	↑ Brain levels of 5-HT	[10]
Fisetin	Male ICR mice	10 and 20 mg/kg (p.o.) 60 min before behavioral test	↓ TTI in FST and TST	↑ 5-HT in frontal cortex and HP	[30]
Vixetin (apigenin-8-C-glucopyranoside)	Adult male BALB/c mice	10, 20, and 30 mg/kg (p.o.) 60 min before behavioral test	↓ TTI in FST and TST	Pretreatment with NAN 190, a 5-HT_{1A} antagonist (0.5 mg/kg, i.p.) prevented antidepressant-like effect of vixetin	[42]
Apigenin	Male ICR mice	7, 10, 14, and 20 mg/kg (p.o.) for 2 weeks	↓ TTI in FST ↑ Sucrose intake	↑ 5-HT in PFC, HP, hypothalamus and nucleus accumbens of rats exposed to CMS	[43]
	Albino mice (either sex)	25 and 50 mg/kg (p.o.) 24, 5, and 1 h before the behavioral test	↓ TTI in TST and FST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of apigenin	[44]
Naringenin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside)	Male ICR mice	10, 20, and 50 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of naringenin	[45]
	Three months old BALB/c male mice	25, 50, and 100 mg/kg (p.o.) for 14 days	↑ Sucrose intake ↓ TTI in FST	↑ 5-HT in cortex and HP	[46]
Silibinin	6–8 weeks old Kunming mice	100, 200, and 400 mg/kg (p.o.) for 3 weeks	↓ TTI in TST and FST	↑ 5-HT in PFC and HP	[47]
	Eight weeks old male Sprague Dawley rats	25, 50, and 100 mg/kg (i.p.) for 14 days	↓ TTI in the FST ↑ Sucrose intake	↑ 5-HT in HP and amygdala, and enhanced expression of TpH-1 mRNA in HP	[48]

Flavonoid	Experimental Subjects	Treatment	Behavioral Effect	Effect on Serotonergic System	Reference
Chrysin	Male C57B/6J mice	5 and 20 mg/kg (p.o.) for 14 days	↓ TTI in FST	↑ 5-HT in HP	[29]
	Adult female C57BL/6 mice	20 mg/kg (p.o.) for 28 days	↓ TTI in FST and TST	↑ 5-HT in PFC and HP	[49]
	Male Wistar rats	5 mg/kg (p.o.) for 28 days	↓ TTI in FST	↓ 5-HT_{1A} and 5-HT_{2A} mRNA in raphe nucleus ↑ 5-HT_{1A} mRNA in HP	[50]
Nobiletin	Male ICR mice	25, 50, and 100 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in FST and TST	Pretreatment with WAY 100,635 (7.1 mg/kg, s.c., a serotonin 5-HT_{1A} receptor antagonist) and cyproheptadine (3 mg/kg, i.p., a serotonin 5-HT_2 receptor antagonist) prevented antidepressant-like effect of Nobiletin	[51]
Liquiritin (7-Hydroxyflavanone 4′-O-glucoside) and Isoliquiritin (2′,4,4′-Trihydroxychalcone 4-glucoside)	Mice	10, 20, and 40 mg/kg (p.o.) 30 min before the behavioral test	↓ TTI in FST and TST	↑ 5-HT in HP, hypothalamus and cortex	[52]

i.p. = intraperitoneally; p.o. = per oral rout; ↑ = the variable was increased; ↓ = the variable was decreased; TTI = total time of immobility; 5-HT = serotonin; HP = hippocampus; PFC = prefrontal cortex; FST = forced swim test; TST = tail suspension test; pCPA = p-chlorophenylalanine methyl ester; CMS = chronic mild stress; 5-HT_{1A} = 5-hydroxytryptamine 1A receptor; 5-HT_{2A} = 5-hydroxytryptamine 2A receptor CUMS = chronic unpredictable mild stress.

Concerning this, hesperidin, a flavonoid abundant in highly consumed citrus fruits such as oranges and lemons, is capable of crossing the BBB [53] and produces anti-inflammatory, antioxidant, and neuroprotective effects [53][54]. It has also been reported to produce antidepressant-like effects in murine models, e.g., the acute or chronic administration of 1 mg/kg hesperidin to mice or chronic administration of 20, 50, and 100 mg/kg hesperidin to rats reduced the immobility time in FST and TST [33][35] and increased sucrose intake [22] and 5-HT concentrations in the HP, PFC, and amygdala [35] [36], while the pretreatment with p-chlorophenylalanine methyl ester (pCPA), a selective inhibitor of tryptophan hydroxylase, an important enzyme in the biosynthesis of serotonin, prevents the antidepressant-like effect of hesperidin [33].

Similarly, in preclinical research on mice, the acute administration of 10 and 20 mg/kg fisetin [30], a flavonoid found in fruits such as apples and strawberries, or acute (10, 20, and 50 mg/kg) [45] or chronic (25, 50, and 100 mg/kg) [46] naringenin, the predominant flavonoid in grapefruit, produces antidepressant-like effects, which are associated with increased 5-HT in the frontal cortex and HP that are abolished through pretreatment with pCPA [31][45][46], which implicates the serotonergic system in its pharmacological and behavioral effects.

In complement, chronic administration of apigenin (7 and 50 mg/kg) [44][45] or (5 and 20 mg/kg) chrysin [49][55], both flavonoids from plants *Passiflora incarnata* and *Matricaria chamomilla*, also increased motivation behaviors—less immobility in FST and TST and higher consumption of sucrose—mediated by the serotonergic system, with higher concentrations of 5-HT in the PFC, HP, and nucleus accumbens, all effects that were prevented by pretreatment with pCPA or ondansetron, a serotonin 5-HT_3 receptor antagonist [43][49][56], important effects if we consider that these brain structures are involved in the physiopathology of depression and are pharmacological targets of antidepressant drugs (i.e., SSRIs, tricyclics, and MAOIs).

The data show that flavonoids have antidepressant-like effects that are related to the modulation of the serotonergic system, similar to that observed with clinical antidepressant drugs, highlighting the potential utility of flavonoids to produce therapeutic effects in humans.

4. BDNF Implicated in the Antidepressant-like Effect of Flavonoids

Several flavonoids exert different mechanisms through which they can modulate the brain-derived neurotrophic factor (BDNF) system and are therefore able to contribute to their antidepressant-like effect [6][57][58]. Among these flavonoids are hesperidin, apigenin, astibilin, bacalein, chrysin, dihydromyricetin, hyperoside, icariin, 7,8-dihydroxyflavone, myricetin, naringenin, naringenin, orientin, and silibinin [28]. **Table 2** summarizes the actions on BDNF related to the antidepressant-like effect of flavonoids.

Table 2. Role of BDNF in the antidepressant-like effect of flavonoids.

Flavonoid	Experimental Subjects	Treatment	Behavioral Effect	Effect on Serotonergic System	Reference
Astilbin (taxifolin-3-O-rhamnoside)	Adult male C57BL/6J mice	10, 20, and 40 mg/kg (i.p.) for 21 days	↓ TTI in FST and TST ↑ Sucrose intake	↑ 5-HT in frontal cortex	[32]
Hesperidin (3,5,7-trihydroxyflavanone-7-rhamnoglucoside)	Male adult Swiss mice	0.1, 0.3, and 1 mg/kg (i.p.) S.D. 30 min before behavioral test	↓ TTI in FST and TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevents antidepressant-like effect	[33]
	Adult male Wistar rats with hyperglycemia induced by streptozotocin	25, 50, and 100 mg/kg (p.o.) for 21 days	↓ TTI in FST	↑ Brain levels of 5-HT	[34]
	Male Swiss Albino mice	1 mg/kg (i.p.) for 14 days	↓ TTI in FST and TST	↑ 5-HT in HP and cerebral cortex	[35]
	Old male Sprague-Dawley rats	20, 50, and 100 mg/kg (i.p.) for 14 days	↑ Sucrose intake ↓ TTI in FST	↑ 5-HT in HP, PFC, and amygdala	[36]
Rutin (quercetin-3-*O*-rhamnosylglucoside)	Male Swiss mice	0.01, 0.1, 0.3, 1, 3, and 10 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in FST	Pretreatment with pCPA (100 mg/kg, i.p.) prevents antidepressant-like effect	[37]
	Five weeks old male Sprague Dawley rats	225 mg/kg (p.o.) for 28 days	↓ TTI ↑ Swimming time in FST	↑ 5-HT in frontal cortex, HP, striatum, and amygdala	[38]
Icariin (7-(β-D-Glucopyranosyloxy)-5-hydroxy-4′-methoxy-8-(3-methylbut-2-en-1-yl)-3-(α-L-rhamnopyranosyloxy) flavone)	Adult male Wistar rats	30 and 60 mg/kg (p.o.) for 5 weeks	↑ Sucrose intake	↑ 5-HT_{1A} mRNA levels in HP and frontal cortex	[39]
Orientin (luteolin-8-C-glucoside)	Adult male Kunming mice	20 and 40 mg/kg (p.o.) 3 weeks	↑ Sucrose intake	↑ 5-HT in HP and PFC	[40]
Hyperoside (quercetin 3-galactoside)	Male Albino Swiss mice	3.75 mg/kg (i.p.) 60 min before the behavioral test	↓ TTI in FST and TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of hyperoside	[41]
Quercetin	Male Swiss Albino mice	25 mg/kg (p.o.) for 4 weeks	↓ TTI in FST and TST	↑ Brain levels of 5-HT	[10]
Fisetin	Male ICR mice	10 and 20 mg/kg (p.o.) 60 min before behavioral test	↓ TTI in FST and TST	↑ 5-HT in frontal cortex and HP	[30]

Flavonoid	Experimental Subjects	Treatment	Behavioral Effect	Effect on Serotonergic System	Reference
Vixetin (apigenin-8-C-glucopyranoside)	Adult male BALB/c mice	10, 20, and 30 mg/kg (p.o.) 60 min before behavioral test	↓ TTI in FST and TST	Pretreatment with NAN 190, a 5-HT_{1A} antagonist (0.5 mg/kg, i.p.) prevented antidepressant-like effect of vixetin	[42]
Apigenin	Male ICR mice	7, 10, 14, and 20 mg/kg (p.o.) for 2 weeks	↓ TTI in FST ↑ Sucrose intake	↑ 5-HT in PFC, HP, hypothalamus and nucleus accumbens of rats exposed to CMS	[43]
	Albino mice (either sex)	25 and 50 mg/kg (p.o.) 24, 5, and 1 h before the behavioral test	↓ TTI in TST and FST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of apigenin	[44]
Naringenin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside)	Male ICR mice	10, 20, and 50 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in TST	Pretreatment with pCPA (100 mg/kg, i.p.) prevented antidepressant-like effect of naringenin	[45]
	Three months old BALB/c male mice	25, 50, and 100 mg/kg (p.o.) for 14 days	↑ Sucrose intake ↓ TTI in FST	↑ 5-HT in cortex and HP	[46]
Silibinin	6–8 weeks old Kunming mice	100, 200, and 400 mg/kg (p.o.) for 3 weeks	↓ TTI in TST and FST	↑ 5-HT in PFC and HP	[47]
	Eight weeks old male Sprague Dawley rats	25, 50, and 100 mg/kg (i.p.) for 14 days	↓ TTI in the FST ↑ Sucrose intake	↑ 5-HT in HP and amygdala, and enhanced expression of TpH-1 mRNA in HP	[48]
Chrysin	Male C57B/6J mice	5 and 20 mg/kg (p.o.) for 14 days	↓ TTI in FST	↑ 5-HT in HP	[29]
	Adult female C57BL/6 mice	20 mg/kg (p.o.) for 28 days	↓ TTI in FST and TST	↑ 5-HT in PFC and HP	[49]
	Male Wistar rats	5 mg/kg (p.o.) for 28 days	↓ TTI in FST	↓ 5-HT_{1A} and 5-HT_{2A} mRNA in raphe nucleus ↑ 5-HT_{1A} mRNA in HP	[50]
Nobiletin	Male ICR mice	25, 50, and 100 mg/kg (p.o.) 60 min before the behavioral test	↓ TTI in FST and TST	Pretreatment with WAY 100,635 (7.1 mg/kg, s.c., a serotonin 5-HT_{1A} receptor antagonist) and cyproheptadine (3 mg/kg, i.p., a serotonin 5-HT_2 receptor antagonist) prevented antidepressant-like effect of Nobiletin	[51]
Liquiritin (7-Hydroxyflavanone 4′-O-glucoside) and Isoliquiritin (2′,4,4′-Trihydroxychalcone 4-glucoside)	Mice	10, 20, and 40 mg/kg (p.o.) 30 min before the behavioral test	↓ TTI in FST and TST	↑ 5-HT in HP, hypothalamus and cortex	[52]

i.p. = intraperitoneally; p.o. = per oral rout; ↑ = the variable was increased; ↓ = the variable was decreased; TTI = total time of immobility; 5-HT = serotonin; HP = hippocampus; PFC = prefrontal cortex; FST = forced swim test; TST = tail suspension test; pCPA = p-chlorophenylalanine methyl ester; CMS = chronic mild stress; 5-HT_{1A} = 5-hydroxytryptamine 1A receptor; 5-HT_{2A} = 5-hydroxytryptamine 2A receptor CUMS = chronic unpredictable mild stress.

According to the above, one of these reported mechanisms is the one that suggests that flavonoids possess a neuroprotective action mediated by the increase in BDNF levels, since they prevent induction of the depressive-like behavior in rodents submitted to depression models (i.e., TST, FST) [31][59][60]. For example, chronic pretreatment with hesperidin (0.3 and 1 mg/kg, i.p., for 21 days) increases the levels of BDNF in HP, which is associated with the decrease in immobility in the FST [16]. It has also been observed that the daily administration of baicalein (10, 20, and 40 mg/kg; i.p.) prior to daily exposure to repeated restraint stress (2 h/day) for 14 days increases BDNF levels and decreases corticosterone concentrations in the HP, which is related to prevention of depressive-like behavior in FST [61].

Moreover, these polyphenolic compounds can increase the expression of BDNF in the brain. In this sense, the antidepressant-like effect of chronic treatment with different flavonoids such as icariin (5 and 10 mg/kg, p.o., for 28 days), naringenin (10 and 20 mg/kg, p.o., for 21 days), silibinin (50 and 100 mg/kg, p.o., for 15 days), and quercetin (10 mg/kg, p.o., for 10 weeks) were associated with increased levels of BDNF mRNA, particularly in brain structures such as HP and PFC [60][62][63][64].

On the other hand, some flavonoids, in addition to regulating BDNF, can also modulate its receptor TrkB [59][60][64][65][66]. For example, chronic treatment with fisetin (5 mg/kg, p.o., for 21 days) increases the TrkB receptor activation in the HP of ICR mice [59]; similarly, sibylinin (50 and 100 mg/kg, p.o., for 15 days) promotes increased expression of this receptor in the HP of male Sprague-Dawley rats [64], actions that were both associated with a decrease in immobility behavior in the FST and TST, which is considered an antidepressant-like effect. These results have significant implications considering that the activity of BDNF and its TrkB receptor can independently regulate the therapeutic effects of conventional antidepressants [67]. The above suggests that flavonoids could exert their therapeutic actions through an alternative mechanism than regulating BDNF levels.

Flavonoids, at preclinical level, can also reverse depressive behaviors by increasing BDNF levels, such as in the case of depressed patients administered antidepressants [15]. For example, astibilin (10, 20, and 40 mg/kg, i.p., for 21 days) reversed the anhedonic behavior in male C57BL/6J induced by chronic stress, which was related to the increase in BDNF levels in the frontal cortex [32]. This same effect has been reported for naringenin (10 and 20 mg/kg, p.o., for 21 days) [47], 7,8-dihydroxyflavone (10 and 20 mg/kg, i.p., for 28 days) [66], and chrysin (5 and 20 mg/kg, p.o., for 28 days) [29], which confirms the potential of flavonoids as possible molecules that could be used for the development of pharmacological prototypes for the treatment of depression.

References

1. Pradier, M.F.; McCoy, T.H., Jr.; Hughes, M. Predicting treatment dropout after antidepressant initiation. Transl. Psychiatry 2020, 10, 60.
2. Simon, G.E.; Savarino, J.; Operskalski, B.; Wang, P.S. Suicide risk during antidepressant treatment. Am. J. Psychiatry 2006, 163, 41–47.
3. Alli, S.R.; Gorbovskaya, I.; Liu, J.; Kolla, N.J.; Brown, L.; Müller, D.J. The gut microbiome in depression and potential benefit of prebiotics, probiotics and synbiotics: A systematic review of clinical trials and observational studies. Int. J. Mol. Sci. 2022, 23, 4494.
4. Kang, M.; Hawken, E.; Vazquez, G.H. The mechanisms behind rapid antidepressant effects of ketamine: A systematic review with a focus on molecular neuroplasticity. Front. Psychiatry 2022, 13, 860882.
5. Pehrson, A.L.; Roberts, D.; Khawaja, A.; McNair, R. The role of serotonin neurotransmission in rapid antidepressant actions. Psychopharmacology 2022, 239, 1823–1838.
6. German-Ponciano, L.J.; Rosas-Sánchez, G.U.; Rivadeneyra-Domínguez, E.; Rodríguez-Landa, J.F. Advances in the preclinical study of some flavonoids as potential antidepressant agents. Scientifica 2018, 2963565, 2963565.
7. Silva, R.F.; Pogačnik, L. Polyphenols from food and natural products: Neuroprotection and safety. Antioxidants 2020, 9, 61.
8. Galanakis, C.M. (Ed.) Polyphenols: Properties, Recovery, and Applications; Woodhead Publishing: Sawston, UK, 2018.
9. Guan, L.P.; Liu, B.Y. Antidepressant-like effects and mechanisms of flavonoids and related analogues. Eur. J. Med. Chem. 2016, 121, 47–57.
10. Khan, K.; Najmi, A.K.; Akhtar, M.A. Natural phenolic compound quercetin showed the usefulness by targeting inflammatory, oxidative stress markers and augment 5-HT levels in one of the animal models of depression in mice. Drug Res. 2019, 69, 392–400.

11. Estrada-Reyes, R.; Ubaldo-Suárez, D.; Araujo-Escalona, A.G. Los flavonoides y el sistema nervioso central. Salud Mental 2012, 35, 375–384.

12. Garg, S.K.; Shukla, A.; Choudhury, S. Nutraceuticals in Veterinary Medicine; Polyphenols and Flavonoids; Springer: Berlin, Germany, 2019; pp. 187–204.

13. Kaeko, M.; Yoshimasa, N.; Mariko, U. Flavonoid metabolism: The interaction of metabolites and gut microbiota. Biosci. Biotechnol. Biochem. 2018, 82, 600–610.

14. Ren, W.; Qian, Z.; Wang, H.; Zhu, L.; Zhang, L. Flavonoids: Promising anticancer agents. Med. Res. Rev. 2003, 23, 519–534.

15. Ko, Y.H.; Kim, S.K.; Lee, S.Y.; Jang, C.G. Flavonoids as therapeutic candidates for emotional disorders such as anxiety and depression. Arch. Pharm. Res. 2020, 43, 1128–1143.

16. Gutierrez-Merino, C.; Lopez-Sanchez, C.; Lagoa, R.; Samhan-Arias, A.; Bueno, C.; Garcia-Martinez, V. Neuroprotective actions of flavonoids. Curr. Med. Chem. 2011, 18, 1195–1212.

17. Imran, M.; Rauf, A.; Shah, Z.A.; Saeed, F.; Imran, A.; Arshad, M.U.; Mubarak, M.S. Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. Phytother. Res. 2019, 33, 263–275.

18. Singh, D.; Hembrom, S. Neuroprotective effect of flavonoids: A systematic review. Int. J. Aging Res. 2019, 2, 26.

19. Xiao, J. Recent advances in dietary flavonoids for management of type 2 diabetes. Curr. Opin. Food Sci. 2022, 44, 100806.

20. Faria, A.; Mateus, N.; Calhau, C. Flavonoid transport across blood-brain barrier: Implication for their direct neuroprotective actions. Nutr. Aging 2012, 1, 89–97.

21. Abd El Mohsen, M.M.; Kuhnle, G.; Rechner, A.R.; Schroeter, H.; Rose, S.; Jenner, P.; Rice-Evans, C.A. Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. Free Radic. Biol. Med. 2002, 33, 1693–1702.

22. Faria, A.; Meireles, M.; Fernandes, I.; Santos-Buelga, C.; Gonzalez-Manzano, S.; Dueñas, M.; Calhau, C. Flavonoid metabolites transport across a human BBB model. Food Chem. 2014, 149, 190–196.

23. Ishisaka, A.; Ichikawa, S.; Sakakibara, H.; Piskula, M.K.; Nakamura, T.; Kato, Y.; Terao, J. Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. Free Radic. Biol. Med. 2011, 51, 1329–1336.

24. Milbury, P.E.; Kalt, W. Xenobiotic metabolism and berry flavonoid transport across the blood-brain barrier. J. Agric. Food Chem. 2010, 58, 3950–3956.

25. Milbury, P.E.; Vita, J.A.; Blumberg, J.B. Anthocyanins are bioavailable in humans following an acute dose of cranberry juice. J Nutr. 2010, 140, 1099–1104.

26. Najmanová, I.; Pourová, J.; Mladěnka, P. A Mixture of phenolic metabolites of quercetin can decrease elevated blood pressure of spontaneously hypertensive rats even in low doses. Nutrients 2020, 12, 213.

27. Abelaira, H.M.; Réus, G.Z.; Quevedo, J. Animal models as tools to study the pathophysiology of depression. Braz. J. Psychiatry 2013, 35, S112–S120.

28. Pannu, A.; Sharma, P.C.; Thakur, V.K.; Goyal, R.K. Emerging role of flavonoids as the treatment of depression. Biomolecules 2021, 11, 1825.

29. Filho, C.B.; Jesse, C.R.; Donato, F.; Giacomeli, R.; Del Fabbro, L.; da Silva Antunes, M.; de Gomes, M.G.; Goes, A.T.; Boeira, S.P.; Prigol, M. 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 2015, 289, 367–380.

30. Zhen, L.; Zhu, J.; Zhao, X.; Huang, W.; An, Y.; Li, S.; Du, X.; Lin, M.; Wang, Q.; Xu, Y.; et al. The antidepressant-like effect of fisetin involves the serotonergic and noradrenergic system. Behav. Brain Res. 2012, 228, 359–366.

31. Donato, F.; de Gomes, M.G.; Goes, A.T.; Filho, C.B.; Del Fabbro, L.; Antunes, M.S.; Souza, L.C.; Boeira, S.P.; Jesse, C.R. Hesperidin exerts antidepressant-like effects in acute and chronic treatments in mice: Possible role of l-arginine-NO-cGMP pathway and BDNF levels. Brain Res. Bull. 2014, 104, 19–26.

32. Lv, Q.Q.; Wu, W.J.; Guo, X.L.; Liu, R.L.; Yang, Y.P.; Zhou, D.S.; Zhang, J.X.; Liu, J.Y. Antidepressant activity of astilbin: Involvement of monoaminergic neurotransmitters and BDNF signal pathway. Biol. Pharm. Bull. 2014, 37, 987–995.

33. Souza, L.C.; de Gomes, M.G.; Goes, A.T.; Del Fabbro, L.; Filho, C.B.; Boeira, S.P.; Jesse, C.R. Evidence for the involvement of the serotonergic 5-HT(1A) receptors in the antidepressant-like effect caused by hesperidin in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 2013, 40, 103–109.

34. El-Marasy, S.A.; Abdallah, H.M.; El-Shenawy, S.M.; El-Khatib, A.S.; El-Shabrawy, O.A.; Kenawy, S.A. Anti-depressant effect of hesperidin in diabetic rats. Can. J. Physiol. Pharmacol. 2014, 92, 945–952.

35. Nadar, J.S.; Kale, P.P.; Kadu, P.K.; Prabhavalkar, K.; Dhangar, R. Potentiation of antidepressant effects of agomelatine and bupropion by hesperidin in mice. Neurol. Res. Int. 2018, 2018, 9828639.

36. Lee, B.; Choi, G.M.; Sur, B. Antidepressant-like effects of hesperidin in animal model of post-traumatic stress disorder. Chin. J. Integr. Med. 2021, 27, 39–46.

37. Machado, D.G.; Bettio, L.E.; Cunha, M.P.; Santos, A.R.; Pizzolatti, M.G.; Brighente, I.M.; Rodrigues, A.L. Antidepressant-like effect of rutin isolated from the ethanolic extract from Schinus molle L. in mice: Evidence for the involvement of the serotonergic and noradrenergic systems. Eur. J. Pharmacol. 2008, 587, 163–168.

38. Lin, S.H.; Chang, H.C.; Chen, P.J.; Hsieh, C.L.; Su, K.P.; Sheen, L.Y. The antidepressant-like effect of ethanol extract of daylily flowers (Jīn Zhēn Huā) in rats. J. Tradit. Complement. Med. 2013, 3, 53–61.

39. Pan, Y.; Wang, F.M.; Qiang, L.Q.; Zhang, D.M.; Kong, L.D. Icariin attenuates chronic mild stress-induced dysregulation of the LHPA stress circuit in rats. Psychoneuroendocrinology 2010, 35, 272–283.

40. Liu, Y.; Lan, N.; Ren, J.; Wu, Y.; Wang, S.T.; Huang, X.F.; Yu, Y. Orientin improves depression-like behavior and BDNF in chronic stressed mice. Mol. Nutr. Food Res. 2015, 59, 1130–1142.

41. Orzelska-Górka, J.; Szewczyk, K.; Gawrońska-Grzywacz, M.; Kędzierska, E.; Głowacka, E.; Herbet, M.; Dudka, J.; Biała, G. Monoaminergic system is implicated in the antidepressant-like effect of hyperoside and protocatechuic acid isolated from Impatiens glandulifera Royle in mice. Neurochem. Int. 2019, 12, 206–214.

42. Can, Ö.D.; Demir-Özkay, Ü.; Üçel, U.İ. Anti-depressant-like effect of vitexin in BALB/c mice and evidence for the involvement of monoaminergic mechanisms. Eur. J. Pharmacol. 2013, 699, 250–257.

43. Yi, L.T.; Li, J.M.; Li, Y.C.; Pan, Y.; Xu, Q.; Kong, L.D. Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin. Life Sci. 2008, 82, 741–751.

44. Al-Yamani, M.J.; Mohammed-Basheeruddin, S.; Alamri, A.S.; Alsanie, W.F.; Alhomrani, M.; Alsalman, A.J.; Al-Mohaini, M.; Al-Hawaj, M.A.; Alanazi, A.A.; Alanzi, K.D.; et al. The role of serotonergic and catecholaminergic systems for possible antidepressant activity of apigenin. Saudi J. Biol. Sci. 2022, 29, 11–17.

45. Yi, L.T.; Li, C.F.; Zhan, X.; Cui, C.C.; Xiao, F.; Zhou, L.P.; Xie, Y. Involvement of monoaminergic system in the antidepressant-like effect of the flavonoid naringenin in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 2010, 34, 1223–1228.

46. Bansal, Y.; Singh, R.; Saroj, P.; Sodhi, R.K.; Kuhad, A. Naringenin protects against oxido-inflammatory aberrations and altered tryptophan metabolism in olfactory bulbectomized-mice model of depression. Toxicol. Appl. Pharmacol. 2018, 355, 257–268.

47. Yan, W.J.; Tan, Y.C.; Xu, J.C.; Tang, X.P.; Zhang, C.; Zhang, P.B.; Ren, Z.Q. Protective effects of silibinin and its possible mechanism of action in mice exposed to chronic unpredictable mild stress. Biomol. Ther. 2015, 23, 245–250.

48. Lee, B.; Choi, G.M.; Sur, B. Silibinin prevents depression-like behaviors in a single prolonged stress rat model: The possible role of serotonin. BMC Complement. Med. Ther. 2020, 20, 70.

49. Bortolotto, V.C.; Pinheiro, F.C.; Araujo, S.M.; Poetini, M.R.; Bertolazi, B.S.; de Paula, M.T.; Meichtry, L.B.; de Almeida, F.P.; de Freitas Couto, S.; Jesse, C.R.; et al. Chrysin reverses the depressive-like behavior induced by hypothyroidism in female mice by regulating hippocampal serotonin and dopamine. Eur. J. Pharmacol. 2018, 822, 78–84.

50. German-Ponciano, L.J.; Rosas-Sánchez, G.U.; Ortiz-Guerra, S.I.; Soria-Fregozo, C.; Rodríguez-Landa, J.F. Effects of chrysin on mRNA expression of 5-HT1A and 5-HT2A receptors in the raphe nuclei and hippocampus. Rev. Bras. Farmacogn. 2021, 31, 353–360.

51. Yi, L.T.; Xu, H.L.; Feng, J.; Zhan, X.; Zhou, L.P.; Cui, C.C. Involvement of monoaminergic systems in the antidepressant-like effect of nobiletin. Physiol. Behav. 2011, 102, 1–6.

52. Wang, W.; Hu, X.; Zhao, Z.; Liu, P.; Hu, Y.; Zhou, J.; Guo, H. Antidepressant-like effects of liquiritin and isoliquiritin from Glycyrrhiza uralensis in the forced swimming test and tail suspension test in mice. Progress in Neuro- Prog. Neuropsychopharmacol. Biol. Psychiatry 2008, 32, 1179–1184.

53. Justin-Thenmozhi, A.; Dhivya Bharathi, M.; Kiruthika, R.; Manivasagam, T.; Borah, A.; Essa, M.M. Attenuation of aluminum chloride-induced neuroinflammation and caspase activation through the AKT/GSK-3β pathway by hesperidin in wistar rats. Neurotox. Res. 2018, 34, 463–476.

54. Herath, H.M.U.L.; Piao, M.J.; Kang, K.A.; Zhen, A.X.; Fernando, P.D.S.M.; Kang, H.K.; Yi, J.M.; Hyun, J.W. Hesperidin exhibits protective effects against PM2.5-mediated mitochondrial damage, cell cycle arrest, and cellular senescence in human HaCaT Keratinocytes. Molecules 2022, 27, 4800.

55. Ahmad, A.; Kumari, P.; Ahmad, M. Apigenin attenuates edifenphos-induced toxicity by modulating ROS-mediated oxidative stress, mitochondrial dysfunction and caspase signal pathway in rat liver and kidney. Pestic. Biochem. Physiol. 201

9, 159, 163–172.

56. Filho, C.B.; Jesse, C.R.; Donato, F.; Del Fabbro, L.; Gomes, M.; Rossito-Goes, A.T.; Souza, L.C.; Boeira, S.P. Chrysin promotes attenuation of depressive-like behavior and hippocampal dysfunction resulting from olfactory bulbectomy in mice. Chem. Biol. Interact. 2016, 260, 154–162.
57. Sharma, P.; Kumar, A.; Singh, D. Dietary flavonoids interaction with CREB-BDNF pathway: An unconventional approach for comprehensive management of epilepsy. Curr. Neuropharmacol. 2019, 17, 1158–1175.
58. Neshatdoust, S.; Saunders, C.; Castle, S.M.; Vauzour, D.; Williams, C.; Butler, L.; Lovegrove, J.A.; Spencer, J.P. High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor: Two randomised, controlled trials. Nutr. Healthy Aging 2016, 4, 81–93.
59. Wang, Y.; Wang, B.; Lu, J.; Shi, H.; Gong, S.; Wang, Y.; Hamdy, R.C.; Chua, B.H.L.; Yang, L.; Xu, X. Fisetin provides antidepressant effects by activating the tropomyosin receptor kinase B signal pathway in mice. J. Neurochem. 2017, 143, 561–568.
60. Wang, G.; Li, Y.; Lei, C.; Lei, X.; Zhu, X.; Yang, L.; Zhang, R. Quercetin exerts antidepressant and cardioprotective effects in estrogen receptor α-deficient female mice via BDNF-AKT/ERK1/2 signaling. J. Steroid. Biochem. Mol. Biol. 2021, 206, 105795.
61. Lee, B.; Sur, B.; Park, J.; Kim, S.-H.; Kwon, S.; Yeom, M.; Shim, I.; Lee, H.; Hahm, D.-H. Chronic administration of baicalein decreases depression-like behavior induced by repeated restraint stress in rats. Korean J. Physiol. Pharmacol. 2013, 17, 393–403.
62. Wu, X.; Wu, J.; Xia, S.; Li, B.; Dong, J. Icaritin opposes the development of social aversion after defeat stress via increases of GR mRNA and BDNF mRNA in mice. Behav. Brain Res. 2013, 256, 602–608.
63. Yi, L.T.; Liu, B.B.; Li, J.; Luo, L.; Liu, Q.; Geng, D.; Tang, Y.; Xia, Y.; Wu, D. BDNF signaling is necessary for the antidepressant-like effect of naringenin. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014, 48, 135–141.
64. Song, X.; Liu, B.; Cui, L.; Zhou, B.; Liu, W.; Xu, F.; Ikejima, T. Silibinin ameliorates anxiety/depression-like behaviors in amyloid β-treated rats by upregulating BDNF/TrkB pathway and attenuating autophagy in hippocampus. Physiol. Behav. 2017, 179, 487–493.
65. Zhao, X.; Kong, D.; Zhou, Q.; Wei, G.; Song, J.; Liang, Y.; Du, G. Baicalein alleviates depression-like behavior in rotenone-induced Parkinson's disease model in mice through activating the BDNF/TrkB/CREB pathway. Biomed. Pharmacother. 2021, 140, 111556.
66. Sawamoto, A.; Okuyama, S.; Yamamoto, K.; Amakura, Y.; Yoshimura, M.; Nakajima, M.; Furukawa, Y. 3,5,6,7,8,30,40-Heptamethoxyflavone, a citrus flavonoid, ameliorates corticosterone-induced depression-like behavior and restores brain-derived neurotrophic factor expression, neurogenesis, and neuroplasticity in the hippocampus. Molecules 2016, 21, 541.
67. Adachi, M.; Autry, A.E.; Mahgoub, M.; Suzuki, K.; Monteggia, L.M. TrkB signaling in dorsal raphe nucleus is essential for antidepressant efficacy and normal aggression behavior. Neuropsychopharmacology 2017, 42, 886–894.