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ANTIDEPRESSANT POTENTIAL OF FLAVONOIDS: A SYSTEMATIC REVIEW

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ABSTRACT

By 2030, depression a major contributor to disability worldwide is expected to rank third in terms of disease burden. Monoamine dysregulation, neuroinflammation, oxidative stress, and reduced neuroplasticity are all involved in its pathogenesis. There is a search for safer natural agents because current antidepressants (TCAs, MAOIs, and SSRIs) are effective but have side effects. The preclinical evidence that flavonoids, including orientin, liquiritin, isoquercitrin, astilbin, and dihydromyricetin, have antidepressant-like effects through HPA axis modulation, BDNF signaling enhancement, MAO inhibition, and neuroinflammation reduction is summarized in this review. Their multitarget profiles indicate that they may be used as primary or supplemental treatments for depression.

KEYWORDS: Depression, Antidepressant, Flavonoids, BDNF, HPA axis.

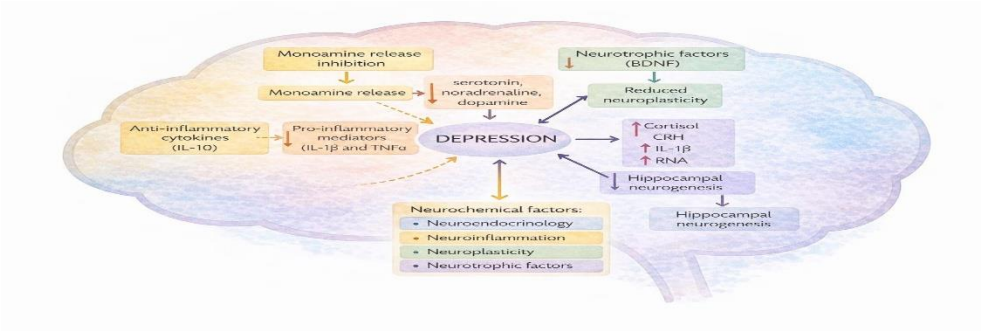
INTRODUCTION

Depression is among the most common mental illnesses in the world. Depression is a potentially fatal illness that affects hundreds of millions of people worldwide. It can occur at any age, from early childhood to old age, and it is very expensive for society because it results in serious and disruption of life, which, if left untreated, can be fatal. Depression is a common illness that compromises mental health and reduces quality of life. Furthermore, by 2030, it is expected to surpass all others as the third-largest contributor to the global burden.[1] Depressive disorders cause significant psychological distress by interfering with both physical and emotional functioning. Common clinical features include persistent low mood, a discernible loss of interest and enjoyment in daily activities, significant changes in body weight without deliberate dieting, changes in psychomotor activity, fatigue or lack in energy, feelings of excessive or guilt or worthlessness, difficulties in concentrating and making decisions, and infrequent thoughts about death.[2] Environmental, biological, and genetic factors all have an impact on depression. Neurotransmitters like 5-hydroxytryptamine, norepinephrine, dopamine, amino-gamma-butyric acid, and glutamate, along with various neurochemicals, hormones, pro-inflammatory cytokines, and other cytokines, all interact and contribute to the complex process.[3] Depression is more common in women than in men, and neurostructural and neurofunctional factors have been proposed as possible causes of this disparity. By changing norepinephrine and serotonin levels in the brain, changes in estrogen secretion, especially during menopause, may have a major impact on the pathophysiology of depression and cause classic symptoms like irritability, melancholy, mood swings, and emotional instability.[4] Over the past few decades, a number of medications, including monoamine oxidase inhibitors and tricyclic antidepressants, have been developed to treat depression[5] and SSRIs, or selective serotonin reuptake inhibitors. Unfortunately, all of the medications have detrimental side effects, such as anxiety, weight gain, and insomnia. It is common knowledge that the best and safest source of all medicines is nature. Therefore, it becomes worthwhile to search for a new approach of antidepressant natural based treatment that has fewer side effects and complications (it is assumed that a natural sources based treatment may have Minimized adverse effects and complications).[6] Based on the knowledge and customs of indigenous cultures, the use and systematization of plants in traditional Mexican medicine has been passed down from generation to generation and has been crucial to its current application in the

prevention and treatment of numerous illnesses. For thousands of years, traditional and folk medicine have used medicinal herbs, and their usefulness in treating mild to moderate illnesses is growing.[7] The disease is one of the main A top cause of global disability. Depression affects women more often than men.[8] There are many biological and therapeutic uses for plants. Their high levels of safety, availability, accessibility, tolerance, and low levels of toxicity make them a great source for creating new medications.[9] Currently, scientists are looking for more targeted medications that are inexpensive, have few side effects, and have high therapeutic efficacy. Scientists in this field are interested in medicinal plants because Used for ages to treat illnesses, with fewer side effects.[10]

Pathophysiology of depression

Reduced monoamine neurotransmitters (serotonin, noradrenaline, and dopamine), increased neuroinflammation, overactivity of the HPA-axis with elevated cortisol, and decreased BDNF are all associated with depression. These alterations cause depressive symptoms by impairing hippocampal neurogenesis and neuroplasticity. According to the classical monoamine hypothesis, depressive disorders are primarily caused by decreased levels or impaired functioning of important mono-amine neurotransmitters, such as, dopamine (DA), and serotonin (5-HT) norepinephrine (NE), in addition to shared pathogenic mechanisms.[11] An essential neurotransmitter that aids in controlling brain activity and flexibility is serotonin. Reduced serotonin and its precursor L-tryptophan are frequently observed in depressed individuals, and low serotonin levels raise the risk of depression.[12,13] Research indicates that the brain's dopamine activity is reduced in those who suffer from depression.[14] The locus coeruleus (LC) releases NE, which can help control a number of brain processes, including movement, smell, and sensation. Depression is more likely when NE levels are lower.[15]



Medicinal Plants, Herbal Medicines, and Their Bioactive Compounds

Herbal medicines, which are in constant demand in both developed and developing nations, are defined by the WHO as preparations and products made from whole plants, plant parts, or other plant materials and their extracts with the goal of therapeutic use or other health benefits.[16] Throughout human history, medicinal plants and herbal remedies have been used to treat illnesses. Approximately 70% of people today use these plants for their low toxicity, though they can have some harmful effects.[17] The creation of new classes of synthetic antidepressants has not advanced significantly in the past ten years. In the meantime, studies on natural product-based psychopharmacology have uncovered numerous promising options for treating depression. Natural alternatives can provide additional safe and effective treatment options, even though synthetic medications and psychological interventions remain the predominant approach.[18] Alkaloids, terpenoids, flavonoids, saponins, tannins, and other chemical compounds found in herbal plants and their parts are used to treat a variety of illnesses. Numerous studies have documented the anti-inflammatory, antidepressant, and antioxidant properties of a number of flavonoids in animal experiments. By influencing transcription factors, enzymes, and kinases, flavonoids contribute to the preservation of the equilibrium of neurotransmitter levels in the brain.[19,26] It has been discovered that flavonoids including Amentoflavone, luteolin, nobiletin, vitexin, fisetin, kaempferitrin, hesperidin,rutin,naringenin and quercetin have antidepressant properties by altering neurotransmitters or by interacting with their pre or post-receptors. On the other hand, it has been discovered that flavonoids like apigenin, luteolin, orientin, hesperidin, quercetin, fisetin, and astilbin raise brain neurotransmitter levels and inhibit the MAO enzyme.[27,34] Plants, fruits, and herbal plants all contain flavonoids, which are low molecular weight phenolic compounds. Over 5000 flavonoids with a wide range of biological activity have been discovered to date.[35]

Flavonoids as the therapeutic option for depression

Numerous pharmacological characteristics of Amentoflavone, a naturally occurring bioflavonoid with position C8, have been demonstrated. Antioxidant, neuroprotective, and anti-inflammatory properties are possible advantages. The Amentoflavone that was extracted from the methanolic root extract of Cnestis ferruginea Vahl ex DC. It exhibits anxiolytic and antidepressant effects in mice, likely mediated by Amentoflavone's interaction with ionotropic and adrenergic GABA receptors (α1- and α2-subtypes) as well as serotonin 5-HT_2 receptors.[36,37] Several studies

have shown that the flavone 7, 8-dihydroxyflavone has antidepressant qualities. It's been recorded. 7,8-Dihydroxyflavone raises BDNF levels in the hippocampus, mimicking the neurotrophic factor, and it exhibits notable oral bioavailability along with efficient blood-brain barrier penetration. Consequently, It was found that this flavone is a great Phytoconstituents for treating depression because It activates the nitric-oxide signaling cascade and stimulates TrkB (tropomyosin-related kinase) receptors.[38,40] Nobiletin is one citrus flavone. This flavone is said to have neuroprotective qualities against β-amyloid. Impairment of cognition, It causes neuronal loss in the hippocampal CA1 area and also lowers β-amyloid peptide levels. The potential of nobiletin as an antidepressant Isolated from orange peel was investigated using FST and TST in animal models found that it significantly reduced depressive-like behaviors. Nobiletin was reported to act on noradrenergic α1-adrenoceptors, dopaminergic D1/D2 receptors, and serotonergic 5-HT1A/5-HT2 receptors.[41,42]

A naturally occurring flavonoid, luteolin has a number of pharmacological characteristics and observed it readily crosses BBB Using animal model of corticosterone-induced depression, Ishisaka. also verified the antidepressant effect of Luteolin exerts its effects by dampening the hippocampal expression of stress-related endoplasmic-reticulum proteins. According to reports, it inhibits the MAO enzyme, which directly causes the brain's neurotransmitter levels to rise in depression.[45] Chrysin, a flavone found in propolis, honey, and various plants, has been shown in numerous studies to have qualities like antidepressant. This flavonoid's capacity to activate neurological factors, The antidepressant-like action of luteolin stems from its ability to curb oxidative-stress markers and modulate apoptotic pathways "Rodríguez-Landa 2022". Research has uncovered multiple mechanisms behind chrysin's potential mood benefits. For instance, chronic chrysin treatment in rats reshaped 5-HT receptor subtype expression in mood-related areas, implying a regulatory effect on serotonin signaling "German-Ponciano 2021". It also appears to boost neurotrophic factors such as BDNF "Jesse, 2015".[46] Baicalein, a 5,6,7-trihydroxyflavone flavonoid bearing hydroxyl groups at the C5, C6, and C7 positions, stands out among the flavones, it is discovered to be one of the most active flavonoid that has been shown to display. Substantial antidepressant effect by raising the degree of decreased ERK phosphorylation And BDNF expression in the hippocampus in an animal model of long-term mild stress Additionally, It has been discovered to cross the blood-brain barrier. Additionally, another study has demonstrated the antidepressant Potential for baicalein to mediate by preventing a drop in dopamine and BDNF levels Within the hippocampus.[47] Apigenin is among the most prevalent flavones in grapefruits, oranges, celery, and onions. Through a variety of mechanisms, it exhibits antidepressant-like effects. The antidepressant potential of Apigenin has been demonstrated by a number of preclinical studies. Using the forced swim test in rodents, researchers have examined apigenin's antidepressant properties and discovered that it reduces Apigenin may alleviate depressive-like behavior in mice by modulating the dopaminergic system, boosting BDNF, and adjusting dopamine and serotonin levels.[48,50,51,52] Hesperidin (4′-methoxy-7-O-rutinosyl-3′,5-dihydroxyflavanone), a citrus flavonoid, produces antidepressant-like effects through multiple pathways: it reduces inflammatory cytokines (IL-6, IL-1β, TNF-α) in stressed mice, and it inhibits K^+ channels, thereby suppressing the L-NAME pathway "Donato et al., 2015". and appears to boost brain dopamine and serotonin levels. These combined effects make hesperidin a promising candidate for adjunctive depression therapy.[53,54] Citrus fruit peel contains a high concentration of naringenin, a trihydroxyflavanone. Three hydroxy groups are structurally substituted at positions C5, C6, and C4′. Its antidepressant effects include upregulating hippocampal BDNF in rodents by stimulating monoamines and suppressing neuro-endocrine signaling. Another study found that naringenin, which was extracted from a citrus peel methanolic extract, had a strong antidepressant effect on mice in study at doses of 5,10 & 20 mg/kg by reducing the duration of immobility in the TST. It has been proposed that this effect involves the mouse brain's noradrenergic and serotonergic monoamine systems being activated.[55,56] Citrus fruits especially grapes are abundant in naringin, a flavanone-7-O-glycoside that imparts their characteristic bitterness "Suseem & Dhanish, 2019". In mice, naringin shows anxiolytic and antidepressant-like activity, boosting social interaction and cutting immobility "Ben Azu 2018". In post-stroke depression models it offers neuroprotection by curbing oxidative stress and boosting mitochondrial function. "Aggarwal, Gaur & Kumar, 2010". Naringin may reduce depressive symptoms associated with neuroinflammation by reducing oxidative damage. Furthermore, it supports neuronal survival and plasticity by inhibiting NMDA receptors and promoting CREB-mediated neurogenesis in the hippocampus.[57,58] Soy isoflavonoid genistein exhibits antidepressant-like properties through multiple pathways. While "Kageyama 2010" connected it to increased serotonin metabolism, "Shen. 2018" reported that it down-regulates miR-221/222, targeting connexin 43. "Hu. 2017" found decreased monoamine oxidase activity in mice along with dose-dependent increases in brain noradrenaline, serotonin, dopamine, and their metabolites. When genistein (10 mg/kg) and amitriptyline (5–10 mg/kg) were combined for 10 days, "Gupta.2015" showed synergistic effects, suggesting utility in treatment-resistant depression. Genistein supplementation A clinical trial showed that it enhanced quality of life and reduced depressive symptoms in post-menopausal women with osteopenia. "Atteritano.,

2014". These results demonstrate the multi-target potential of genistein and encourage more research.[59]

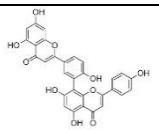
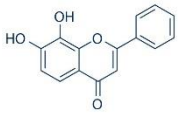
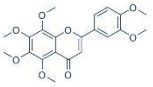
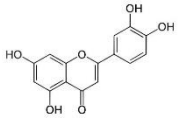
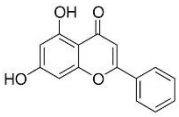
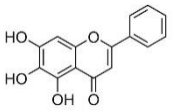
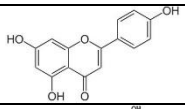
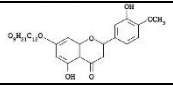
In rodent models, daidzein, a soy isoflavone that can be converted to the more estrogenic equol, has demonstrated antidepressant-like properties. "Chen.2021" discovered that daidzein decreased immobility in chronically stressed mice and reversed learned-helplessness behavior in rats, It likely works by dampening HPA-axis hyperactivity and partially restoring inflammatory cytokine levels.[60] Preclinical research has revealed Rutin, a citrus bioflavonoid, emerges as a potential depression therapy. Research by Machado et al. reveals that an ethanolic Schinus molle extract rich in rutin exerts antidepressant-like effects, likely via enhanced noradrenaline and serotonin availability. Rutin elicited a dose-dependent reduction in immobility time in the mouse tail suspension test (TST) further supporting the antidepressant potential of rutin. These studies demonstrate rutin's potential for treating depression. To determine a safe and tolerable dosage schedule and to clarify the exact mechanisms of action, more research is required. Furthermore, investigating possible adverse effects and drug interactions is essential for ethical clinical development.[62,63] A flavonoid found In tea, broccoli, tomatoes, Ginkgo biloba, grapes, and other plant foods. Preclinical work shows it reduces immobility in rodent depression models "Park 2010" and produces antidepressant-like effects under chronic stress via anti-inflammatory and antioxidant pathways linked to AKT/β-catenin signaling "Gao 2019". A study isolating kaempferol-3-O-D-glucoside, kaempferol, quercetin, and quercetin-3-O-D-glucoside from Apocynum venetum leaves also reported improved depressive-like behavior. This was linked to increased serotonin, dopamine, and norepinephrine as well as decreased serotonin turnover "Yan., 2015". To verify efficacy and tolerability in humans, more SAR research, safety evaluations, and clinical trials are required.[64]

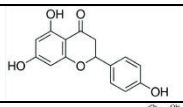
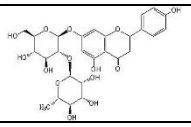
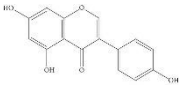
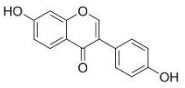
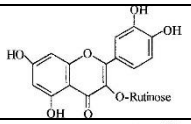
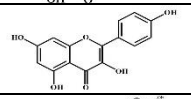
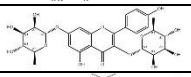
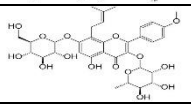
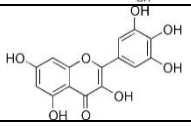
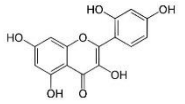
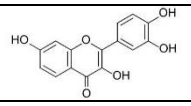
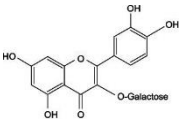
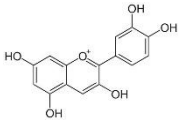
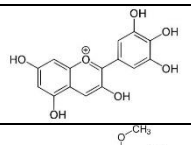
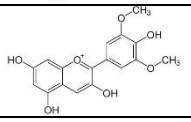
Kaempferitrin, a dirhamnoside of kaempferol with hydroxyl groups substituted at positions 3 and 7, occurs in plants such as Justicia spicigera (Asteraceae). Treatment with kaempferitrin has been found to improve performance of depressed mice in the forced-swim and tail-suspension tests. Kaempferitrin acts as an antidepressant at the molecular level. Potential by adjusting the serotonergic system's activity, especially via presynaptic 5-HT1A receptors and controlling HPA stands for hypothalamic-hypophysis-adrenal axis.[65] Herbal epimedii contains a lot of icariin, a prenylated flavonol glycoside that is derived from kaempferol and has demonstrated antidepressant-like effects in animal models. HPA-axis balance is restored, BDNF is increased, neuroinflammation and nitric oxide are suppressed, and NF-κB, SGK1, and FKBP5 signaling are inhibited "Wu., 2013; Liu., 2015; Wei., 2016" Increased monoamine neurotransmitters and activation of BDNF-TrkB pathway have been reported into recent work "Di., 2023" To verify safety and effectiveness in humans, more structure-activity research and clinical trials are required.[67] A hexahydroxyflavone found In many fruits, vegetables, nuts, tea, and red wine, myricetin exhibits antidepressant-like effects in mice. After repeated restraint stress, "Ma.2015" found decreased plasma corticosterone, increased hippocampal glutathione peroxidase activity, and decreased immobility in the tail-suspension test. "Meyer.2017" discovered that 10 mg/kg myricetin increased mobility in the TST, most likely through nitric oxide inhibition and hippocampal neurogenesis.[68] Preclinical research indicates that the naturally occurring flavonoid morin may have antidepressant properties. Morin treatment decreased inflammatory markers Morin treatment lowered levels of tumor necrosis factor-alpha, toll-like receptor-4, NOD-like receptor pyrin domain-containing protein-3, interleukin-1β and caspase-1 in the brain, while also decreasing the apoptotic marker caspase-3. It raised brain concentrations of epinephrine, norepinephrine and 5-HT in a chronic-stress model, suggesting antidepressant action through anti-inflammatory and neurochemical routes "Hassan 2020" Conversely, "Ben-Azu 2019" reported that L-arginine, a nitric-oxide precursor, reversed Morin's antidepressant effects in mice, indicating that morin may act via the nitric-oxide pathway, potentially inhibited by N(G)-nitro-L-arginine methyl ester (L-NAME).[69] In rodents, the strawberry-derived flavonoid fisetin (7,3′,4′-flavon-3-ol) produces antidepressant-like effects. Its actions include monoamine oxidase inhibition, heightened noradrenergic and serotonergic tone, and activation of TrkB signaling without altering total TrkB levels. Antioxidant and anti-inflammatory activities further support its neuroprotective benefits. To apply these findings to humans, more research is required.[70] In rodents, hyperoside, the 3-O-galactoside of quercetin, exhibits antidepressant-like properties. While "Haas.2011" proposed D2-dopamine receptor activation, "Zheng.2012" connected it to up-regulated CREB/BDNF via the AC-cAMP-CREB pathway. Further research reveals HPA-axis modulation, which lowers ACTH and corticosterone.[71] For seven days, post-stroke depressed male mice were used to test the effects of maqui berry extract (MBE) containing cyanidin and delphinidin dose of 25, 50, and 100 mg/kg. Anhedonia immobility time were reduced in mice treated with MBE. It's interesting to note that MBE increased antioxidant enzymes and decreased elevated TBARS levels "Abdul Rahman 2015" Thus, Reducing oxidative stress can restore normal behavior in mice "Di Lorenzo 2019" Red wine supplies the anthocyanin malvidin, which protects neurons against oxidative damage in cell cultures and animal models "Khoo 2017" Since malvidin-3′-O-glucoside crosses the blood-brain barrier and boosts Rac1 expression in the nucleus accumbens "Wang et al.2018" a protein whose loss contributes to synaptic deficits in depression "Golden et al 2013" it may

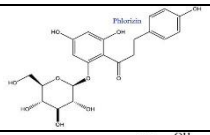
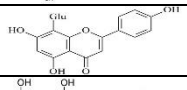
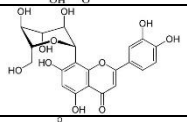
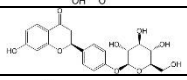
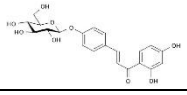
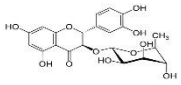
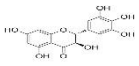
help normalize brain circuitry administration of this drug has been shown to attenuate depressive-like behavior.[74]

Phloridzin‑rich apple peels represent a novel avenue for depression treatment "Dhalaria 2020, Kamdi, Raval, and Nakhate 2021" reported that phloridzin improves mobility in diabetic mice, a behavioral indicator of reduced depressive‑like symptoms. The compound also restored levels of key biochemical markers associated with depression including GSH, BDNF, TrkB, CREB, and ERK. These findings underscore the need for further investigation into phloridzin's therapeutic potential. Especially in diabetic patients.[75] Preclinical research has shown that vitexin, a C-glycosylated apigenin-type flavone found in Passiflora incarnata, has anxiolytic and antidepressant-like properties. In addition to increasing synaptic neurotransmitter levels, its activity seems to be associated with modulation of dopaminergic (D1–D3), serotonergic (5–HTA), and noradrenergic (α_2) receptors. Vitexin has antitumor, anti-inflammatory, antioxidant, and enzyme-inhibitory properties in addition to its effects on mood.[76] In chronically stressed mice, oriententin, a C-glycosyl luteolin found in fruits, herbs, and millet, exhibits antidepressant-like effects. It seems to function by blocking MAO, increasing neurotransmitter levels, It raises synaptic proteins and BDNF in the hippocampus and prefrontal cortex, thereby enhancing neuroplasticity and transmission while lowering oxidative stress.[77] At 10–40 mg/kg, the flavonoids liquiritin and isoliquiritin from Glycyrrhizauralensis exhibit antidepressant like activity Using mice. Their effects are associated with It raises serotonin and norepinephrine levels in the cortex, hypothalamus, and hippocampus while slowing 5‑HT turnover, as indicated by a lower 5‑HIAA/5‑HT ratio.[78-79] Astilbin, a taxifolin-α-L-rhamnoside that is abundant in Hypericum perforatum, exhibits antidepressant-like properties. The effect seems to be associated with increased neurotransmitter release and up-regulated BDNF signaling, most likely through MAO inhibition.[80]Ampelopsis, Hovenia, and a number of other plants contain dihydromyricetin (ampelopsin), a highly hydroxylated flavanonol that exhibits antidepressant-like effects in rodents. "Ren Z" The effect was linked to higher BDNF expression and reduced neuro‑inflammation.[81]

Summary of Flavonoids as a therapeutic option for depression

No	Name	Mechanism	Structure	Author	Reference
1	Amentoflavone	↑5‑HT_2 → serotonin boost- α_1/α_2 → norepinephrine lift		Ishola 2012	36-37
2	7,8-Dihydroxyflavone	TrkB receptor agonist → mimics BDNF, ↑ Hippocampal BDNF → synaptic plasticity, mood lift, Activates *PI3K/Akt/mTOR/ERK pathway		Zhang 2016,Amin 2020	38-40
3	Nobiletin	LPS-induced neuroinflammation through inhibition of the NLRP3 inflammasome via AMPK Autophagy decreases depressive-like behavior (TST, FST). Modifies the signaling of monoamines, including NE, DA, 5HT.		"Yi 2011"	41,42
4	Luteolin	normalizes HPA axis (↓ corticosterone/ACTH) - ↑ serotonin, ↓ norepinephrine in PFC/hippocampus, restores synapsin & synaptogenesis		"Sur & Lee, 2022", "Ishisaka 2011","de la Pena 2014"	43-45
5	Chrysin	↑ serotonin, BDNF, GABA; ↓ oxidative stress		"Jesse 2015", "Cueto-Escobedo 2020"	46
6	Baicalein	↑BDNF/ERK, ↓NF‑κB, ↑dopamine, ↑cAMP/PKA		"Xiong 2011","Lee 2013","hang 2018"	47
7	Apigenin	↓ inflammation, ↑ serotonin/dopamine, ↑ BDNF		Nakazawa 2003,Yi 2008, Weng 2016	48-52
8	Hesperidin	↑ monoamines & BDNF, ↓ ROS & L‑arginine‑NO‑cGMP		Salma a El-Marasy 2014	53-54

9	Naringenin	↑ noradrenaline & serotonin → monoamine boost,↑ hippocampal BDNF ,reduces neuro-stress		Yi 2010, Yi 2014, Zhang 2023	55-56
10	Naringin	↓ TNF-α, IL-1β & corticosterone, antioxidant, ↑ 5-HT		Ben-Azu 2018	57-58
11	Genistein	↓ miR-221/222 → ↑ connexin 43, ↑ monoamines (5-HT, NA, DA) & ↓ MAO		Hu 2017, Gupta 2015	59
12	Daidzein	↓ HPA-axis hyperactivity & inflammatory cytokines, restore monoamine balance		Setchell Brown & Lydeking Olsen 2002 ,Chen 2021	60
13	Rutin	↑ synaptic noradrenaline & serotonin		Machado 2008, Yusha 2017	61-63
14	Kaempferol	↑ monoamines level		Yan 2015	64
15	Kaempferitrin	↑ presynaptic 5-HT1A activity & serotonin, ↓ HPA axis		Cassani 2014	65
16	Icariin	↑ BDNF-TrkB & monoamines, ↓ HPA-axis, NF-κB, SGK1/FKBP5		Wu.2013, Liu 2015 & Di 2023	66-67
17	Myricetin	↑ hippocampal GSH-PX & neurogenesis, ↓ plasma corticosterone level		Ma 2015	68
18	Morin	↑ monoamines (NE, 5-HT, DA), ↓ inflammation & oxidative stress, modulate BDNF/CREB		Sahin 2019 ,Samad.2018, Yan 2015 Hou 2010	69
19	Fisetin	↑ serotonin & noradrenaline, (↓TNF-α/NLRP3), activate TrkB		Zhen 2012,Gopnar 2023	70
20	Hyperoside	↑ D2-dopamine, BDNF/CREB via AC-cAMP, ↓ HPA axis, inhibit NLRP1 inflammasome (CXCL1/CXCR2)		Haas 2011,Song 2022	71
21	Cyanidin	↑ monoamines (NE, DA, 5-HT) via MAO-inhibition; ↑ BDNF, neurogenesis (PI3K/AKT/FoxG1/FGF-2); ↓ oxidative stress, restore GFAP, GLAST/EAAT2		Fang 2020 ,Shan 2020	72
22	Delphinidin	↓ oxidative stress (↓TBARS, ↑ enzymes antioxidant		Abdul Rahman 2015	73
23	Malvidin	improving synaptic structure		Golden 2013	74

24	Phlioridzin	TrkB, CREB & ERK → neuro‑protective ,↑ BDNF		Raval & Nakhate 2021	75
25	Vitexin	↑ DA, 5‑HT, NE via D1/D2/D3, 5‑HT1A, α2 receptors		Özgür Devrim Can 2013	76
26	Orientin	↑ DA, 5‑HT, NE via D1/D2/D3, 5‑HT1A, α2 receptors		Y Wang 2015	77
27	Liquiritin	↓ 5‑HT metabolism → ↑ serotonin, ↑ NE in cortex		X.; Zhao, Z.; Liu 2008	78
28	Isoliquiritin.	↓ cortisol/ACTH via HPA‑axis modulation		V.; Hegger, M.; Winterhoff, H 2004	79
29	Astilbin	↑ BDNF signaling & neurotransmitter release in cortex, Inhibits MAO → ↑ monoamines		Qiong-Qiong Lv 2014	80
30	Dihydromyricetin	↑ BDNF		Yan, P.; Zhu, L Yang 2018	81

CONCLUSION

Depression remains a significant public health issue, and the limitations of synthetic antidepressants highlight the need for safer alternatives. Flavonoid-rich plant extracts have consistently demonstrated antidepressant-like effects in animal models through various mechanisms. Their favorable safety profile and accessibility make them promising candidates for therapeutic development. Future research should focus on thorough pharmacokinetic studies, dose-response optimization, and controlled clinical trials to convert these preclinical findings into efficient, affordable treatment options for depressive disorders.

REFERENCE

1 N. Bains, S. Abdijadid, Major Depressive Disorder, StatPearls Publishing,Treasure Island, 2024.

2 Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. Dialogues Clin Neurosci, 2008; 10(3): 271-7. Doi: 10.31887/DCNS.2008.10.3/shkennedy.

3 Ekong MB, Iniodu CF. Nutritional therapy can reduce the Burden of depression management in low income countries: A review. IBRO Neurosci Rep, 2021; 11: 15-28. Doi: 10.1016/j.Ibneur.2021.06.002.

4 Salomão J. O., Silvério V., de Siqueira I., Cabral D., Acosta R. J. D. L. T., Xavier G., de Matos A., Lopes E., and Xavier A., Influence of Gut Microbiota and Nutrition on Depression in Women: A Systematic Review, Brazilian Journal of Health Review, 2021; 4(2): 5622–5638, https://doi.org/10.34119/bjhrv4n2-128.

5 Zhang ZJ. Therapeutic effects of herbal extracts and constituents in animal models of psychiatric disorders. Life Sci, 2004; 75: 1659–99.

6 Satyavati GV, Raina MK, Sharma M. Chemical investigation of Herpestis monniera Linn (Brahmi). Indian J Pharmacology, 1976; 21: 303–4.

7 Joshi D, Gohil KJ, "A Brief Review on Murraya paniculata (Orange Jasmine): pharmacognosy, phytochemistry and ethanomedicinal Uses" J Pharmacopuncture, 2023; 26(1): 10-17. PMID: 37007290; PMCID: PMC10063420. https://doi.org/10.3831/KPI.2023.26.1.10

8 World Health Organization, "Depression" Available online: https://www.who.int/news-room/fact-sheets/detail/depression

9 Behl T, Singh S, Sharma N, Zahoor I, Albarrati A, Albratty M, Meraya AM, Najmi A, Bungau S, Expatiating the Pharmacological and Nanotechnological Aspects of the Alkaloidal Drug Berberine: Current and Future Trends. Molecules, 2022; 27: 3705. https://doi.org/10.3390/molecules27123705

10 Rabiei Z, Rabiei S. A review on antidepressant effect of medicinal plants. Bangladesh J Pharma, 2017; 12(1): 1-11.

11 Bhatt, S., Devadoss, T., Manjula, S. N. & Rajangam, J. 5-HT(3) receptor antagonism A potential therapeutic approach for the treatment of depression and other Disorders. Curr. Neuropharmacol, 2021; 19: 1545–1559.

12 Martin, H. Insulin modulates emotional behavior through a serotonin-Dependent mechanism. Mol. Psychiatry, 2022.

13 Ogawa, S. Plasma L-tryptophan concentration in major depressive dis-Order: new data and meta-analysis. J. Clin. Psychiatry, 75: e906–915.

14 Bekhbat, M. Correction to: functional connectivity in reward circuitry and Symptoms of anhedonia as therapeutic targets in depression with high inflammation: evidence from a dopamine challenge study. Mol. Psychiatry, 27: 4122.

15 Breton-Provencher, V., Drummond, G. T., Feng, J., Li, Y. & Sur, M. Spatiotemporal Dynamics of

noradrenaline during learned behaviour. Nature, 2022; 606: 732–738.
16 Bareetseng S., The Worldwide Herbal Market: Trends and Opportunities, Journal of Biomedical Research & Environmental Sciences, 2022; 3: no. 5, 575–584, https://doi.org/10.37871/jbres1482.
17 Yuan X, Chapman RL, Wu Z. Analytical methods for heavy metals in herbal medicines. Phytochemical Anal, 2011; 22(3): 189-98.
18 Korczak M., Pilecki M., Granica S., Gorczynska A., Pawłowska K. A., and Piwowarski J. P., Phytotherapy of Mood Disorders in the Light of Microbiota-Gut-Brain Axis, Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 2023; 111: 154642, https://doi.org/10.1016/j.phymed.2023.154642, 36641978.
19 Hritcu, L.; Ionita, R.; Postu, P.A.; Gupta, G.K.; Turkez, H.; Lima, T.C.; Carvalho, C.U.S.; de Sousa, D. Antidepressant Flavonoids And Their Relationship with Oxidative Stress. Oxidative Med. Cell. Longev, 2017; 2017: 1–18.
20 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. Pharmacal Res, 2020; 43: 1128–1143.
21 Spencer, J.P. Flavonoids and brain health: Multiple effects underpinned by common mechanisms. Genes Nutr. 2009, 4, 243–250. Biomolecules, 2021; 11: 1825 47 of 49
22 Hasler, G. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World J. Psychiatry, 2010; 9: 155–161.
23 Nutt, D.J. Relationship of neurotransmitters to the symptoms of major depressive disorder. J. Clin. Psychiatry, 2008; 69: 4–7.
24 Aan het Rot, M.; Mathew, S.J.; Charney, D.S. Neurobiological mechanisms in major depressive disorder. CMAJ., 2009; 180: 305–313.
25 Brigitta, B. Pathophysiology of depression and mechanisms of treatment. Dialogues Clin. Neurosci, 2002; 4: 7–20.
26 Kumar, G.P.; Khanum, F. Neuroprotective potential of phytochemicals. Pharm. Rev, 2012; 6: 81–90.
27 Shola, I.; Chatterjee, M.; Tota, S.; Tadigopulla, N.; Adeyemi, O.O.; Palit, G.; Shukla, R. Antidepressant and anxiolytic effects of Amentoflavone isolated from Cnestis ferruginea in mice. Pharmacol. Biochem. Behav, 2012; 103: 322–331.
28 De la Peña, J.B.; Kim, C.A.; Lee, H.L.; Yoon, S.Y.; Kim, H.J.; Hong, E.Y.; Kim, G.H.; Ryu, J.H.; Lee, Y.S.; Kim, K.M.;. Luteolin Mediates the antidepressant-like effects of Cirsium japonicum in mice, possibly through modulation of the GABA-A receptor. Arch.Pharm. Res, 2014; 37: 263–269.
29 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. Physio. Behav, 2011; 102: 1–6.
30 can, O.D.; Ozkay, U.D.; Uçel, U.I. Anti-depressant like effect of vitexin in BALB/c mice and evidence for the involvement of Monoaminergic mechanisms. Eur. J. Pharm, 2013; 699: 250–257.
31 Zhen, L.; Zhu, J.; Zhao, X.; Huang, W.; An, Y.; Li, S.; Du, X.; Lin, M.; Wang, Q.; Xu, Y. The antidepressant-like effect of fisetin involves the serotonergic and noradrenergic system. Behav. Brain Res., 2012; 228: 359–366.
32 Cassani, J.; Dorantes-Barrón, A.; Novales, L.; Real, G.; Estrada-Reyes, R. Anti-depressant-like effect of kaempferitrin isolated from Justicia spicigera Schltdl (Acanthaceae) in two behavior models in mice: Evidence for the involvement of the serotonergic system. Molecules, 2014; 19: 21442–21461.
33 Yan, S.-X.; Lang, J.-L.; Song, Y.-Y.; Wu, Y.-Z.; Lv, M.-H.; Zhao, X.; Liu, Y.-H.; Xu, C.-Y. Studies on anti-depressant activity of four Flavonoids isolated from Apocynum venetum Linn (Apocynaceae) leaf in mice. Trop. J. Pharm. Res, 2015; 14: 2269–2277.
34 El-Marasy, S.A.; Abdallah, H.M.I.; 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. Pharm, 2014; 92: 945–952.
35 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: 1–14.
36 Kim, H.K.; Son, K.H.; Chang, H.W.; Kang, S.S.; Kim, H.P. Amentoflavone, a plant biflavone: A new potential anti-inflammatory agent. Arch. Pharm. Res, 1998; 21: 406–410.
37 Ishola, I.; Chatterjee, M.; Tota, S.; Tadigopulla, N.; Adeyemi, O.O.; Palit, G.; Shukla, R. Antidepressant and anxiolytic effects of Amentoflavone isolated from Cnestis ferruginea in mice. Pharmacol. Biochem. Behav, 2012.
38 Zhang, L.M.; Wang, H.L.; Zhao, N.; Chen, H.X.; Li, Y.F.; Zhang, Y.Z. Involvement of nitric oxide (NO) signaling pathway in the Antidepressant action of the total flavonoids extracted fromXiaobuxin-Tang. Neurosci. Lett, 2014; 575: 31–36.
39 Zhang, M.W.; Zhang, S.F.; Li, Z.H.; Han, F. 7,8-Dihydroxyflavone reverses the depressive symptoms in mouse chronic mild stress.Neurosci. Lett, 2016; 635: 33–38.
40 Liu, X.; Qi, Q.; Xiao, G.; Li, J.; Luo, H.R.; Ye, K. O-methylated metabolite of 7,8-dihydroxyflavone activates TrkB receptor and Displays antidepressant activity. Pharmacology, 2013; 91: 185–200.
41 Matsuzaki, K.; Yamakuni, T.; Hashimoto, M.; Haque, A.M.; Shido, O.; Mimaki, Y.; Sashida, Y.; Ohizumi, Y. Nobiletin restoring B-amyloid-impaired CREB phosphorylation rescues memory deterioration in Alzheimer's disease model rats. Neurosci. Lett, 2006; 400: 230–234.
42 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. Physio. Behav, 2011; 102: 1–6.
43 Ishisaka, M.; Kakefuda, K.; Yamauchi, M.; Tsuruma, K.; Shimazawa, M.; Tsuruta, A.; Hara, H. Luteolin shows an antidepressant-Like effect via suppressing endoplasmic reticulum stress. Bio Pharm Bull, 2011; 34: 1481–1486.
44 de la Peña, J.B.; Kim, C.A.; Lee, H.L.; Yoon, S.Y.; Kim, H.J.; Hong, E.Y.; Kim, G.H.; Ryu, J.H.; Lee, Y.S.; Kim, K.M.;. Luteolin Mediates the antidepressant-like effects of Cirsium japonicum in mice, possibly through modulation of the GABA-A receptor. Arch.Pharm. Res, 2014; 37: 263–269.
45 Recalde-Gil, M.A.; Klein-Junior, L.C.; Passos, C.D.S.; Salton, J.; Bordignon, S.A.L.; Monace, F.D.; Cechinel, V.; Teresi'ha Henriquesa, Monoamine oxidase inhibitory activity of biflavonoids from branches of Garcinia gardneriana (Clusiaceae). Nat. Prod. Commun, 2017; 12: 505–508.
46 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.
47 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.
48 Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kr˛egiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino,E.. The Therapeutic Potential of Apigenin. Int. J. Mol. Sci, 2019; 20: 1305.
49 Nakazawa, T.; Yasuda, T.; Ueda, J.; Ohsawa, K. Antidepressant-like effects of apigenin and 2,4,5-trimethoxycinnamic acid from Perilla frutescens in the forced swimming test. Biol. Pharm. Bull, 2003; 26: 474–480.
50 Li, R.; Wang, X.; Qin, T.; Qu, R.; Ma, S. Apigenin ameliorates chronic mild stress-induced depressive behavior by inhibiting Interleukin-1β production and NLRP3 inflammasome activation in the rat brain. Behav. Brain Res, 2016; 296: 318–325.
51 Weng, L.; Guo, X.; Li, Y.; Yang, X.; Han, Y. Apigenin reverses depression-like behavior induced by chronic corticosterone treatment In mice. Eur. J. Pharm, 2016; 774: 50–54.
52 Recalde-Gil, M.A.; Klein-Junior, L.C.; Passos, C.D.S.; Salton, J.; Bordignon, S.A.L.; Monace, F.D.; Cechinel, V.; Teresi'ha Henriquesa, Monoamine oxidase inhibitory activity of biflavonoids from branches of Garcinia gardneriana (Clusiaceae). Nat. Prod. Commun, 2017; 12: 505–508.
53 Filho, C.B.; Del Fabbro, L.; de Gomes, M.G.; Goes, A.T.; Souza, L.C.; Boeira, S.P.; Jesse, C.R. Kappa-opioid receptors mediate the Antidepressant-like activity of hesperidin in the mouse forced swimming test. Eur. J. Pharm, 2013; 698: 286–291.
54 Souza, L.C.; de Gomes, M.G.; Goes, A.T.; Del Fabbro, L.; Carlos Filho, 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.
55 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.
56 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.
57 Suseem, S.R.; Joseph, D. The myth and the fact on naringin—A review. Res. J. Pharm. Tech. 2019, 12, 367–374.
58 Chen, R.; Qi, Q.L.; Wang, M.T.; Li, Q.Y. Therapeutic potential of naringin: An overview. Pharm Biol, 2016; 54: 3203–3210.
59 Hu 2017; Kageyama, 2010.
60 Chen, 2021.
61 Ganeshpurkar, A.; Saluja, A.K. The Pharmacological Potential of Rutin. Saudi Pharm. J., 2017; 25: 149–164.
62 Al-Dhabi, N.A.; Arasu, M.V.; Park, C.H.; Park, S.U. An up-to-date review of rutin and its biological and pharmacological activities.Excli. J., 2015; 14: 59–63.
63 Gullón, B.; Lú-Chau, T.A.; Moreira, M.T.; Lema, J.M.; Eibes, G. Rutin: A review on extraction, identification and purification Methods, biological activities and approaches to enhance its bioavailability. Trends Food Sci. Tech, 2017; 67: 220–235.
64 an, S.-X.; Lang, J.-L.; Song, Y.-Y.; Wu, Y.-Z.; Lv, M.-H.; Zhao, X.; Liu, Y.-H.; Xu, C.-Y. Studies on anti-depressant activity of four flavonoids isolated from Apocynum venetum Linn (Apocynaceae) leaf in mice. Trop. J. Pharm. Res, 2015; 14: 2269–2277.
65 Cassani, J.; Dorantes-Barrón, A.; Novales, L.; Real, G.; Estrada-Reyes, R. Anti-depressant-like effect of kaempferitrin isolated from Justicia spicigera Schltdl (Acanthaceae) in two behavior models in mice: Evidence for the involvement of the serotonergic system. Molecules, 2014; 19: 21442–21461.
66 Liu, B.; Xu, C.; Wu, X.; Liu, F.; Du, Y.; Sun, J.; Tao, J.; Dong, J. 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, 2015; 294: 193–205.

67 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.

68 Ma, Z.; Wang, G.; Cui, L.; Wang, Q. Myricetin attenuates depressant-like behavior in mice subjected to repeated restraint stress.Int. J. Mol. Sci, 2015; 16: 28377–28385.

69 Hou, 2010.

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

71 Zheng, M.; Liu, C.; Pan, F.; Shi, D.; Zhang, Y. Antidepressant-like effect of hyperoside isolated from Apocynum venetum leaves:Possible cellular mechanisms. Phytomedicine, 2012; 19: 145–149.

72 Shan, 2020, Qu, 2022.

73 Di Lorenzo, 2019.

74 Khoo, 2017.

75 Dhalaria 2020, Kamdi, Raval, and Nakhate, 2021.

76 Can, O.D.; Ozkay, U.D.; Uçel, U.I. Anti-depressant like effect of vitexin in BALB/c mice and evidence for the involvement of monoaminergic mechanisms. Eur. J. Pharm, 2013; 699: 250–257.

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

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

79 Butterweck, V.; Hegger, M.; Winterhoff, H. Flavonoids of St. John'sWort reduce HPAaxis function in the rat. Planta Med, 2004; 70: 1008–1011.

80 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.

81 Ren, Z.; Yan, P.; Zhu, L.; Yang, H.; Zhao, Y.; Kirby, B.P.; Waddington, J.L.; Zhen, X. Dihydromyricetin exerts a rapid antidepressant-Like effect in association with enhancement of BDNF expression and inhibition of neuroinflammation. Psychopharmacology, 2018; 235: 233–244.