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Current standing of plant derived flavonoids as an antidepressant

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ABSTRACT

Depression, a multifactorial brain disorder, is one of the most prevalent diseases worldwide. Several strategies have been developed to counteract the main symptoms and disorders. However, the treatments are usually associated with different side effects or poor effect. For that reason, new necessary approaches are emerging; among them, natural products are good alternatives since no interactions have been described up to now. Flavonoids have been related to antidepressant effects in cell lines and animal models by their action on the amine mechanisms protecting the neuroendocrine and immune systems. The current review includes an approach of some of the main results related to the action of flavonoids on depression found in the literature and a short view of the possible mechanisms involved. Thus, it highlights the potential emerging candidates with strong antidepressant effects which could be effective new compounds.

1. Introduction

The current life rhythm associated to the new societies can lead to the development of depression after a change in the nervous and immune system functions. The most prevalent mental disorder recognized to be symptomatically, psychologically and biologically heterogeneous is depression (Bugel and Tanguay, 2018; Nabavi et al., 2017; Rauf et al., 2016). Some characteristics related to depressive disorder include those found in anxiety disorders, such as severe phobias, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder, and obsessive-compulsive disorder (Frandsen and Narayanasamy, 2018). An assumption is made about depression that it will be considered as the global burden of diseases by 2030, on the basis of serious limitations in its existing treatment regarding the therapeutic success, safety, efficacy and tolerability (Abbas, 2014). Depression has been identified as a chronic and disabling mental illness which is a leading cause of morbidity and mortality worldwide (Carde et al., 2016; Gaffrey and Barch, 2013; M.P. Kaster et al., 2016). In this sense, approximately 20% of population at United States suffers from depression. Moreover, in severe, vital, or melancholic depression physical changes also occur, including insomnia or hypersomnia, altered feeding patterns related to overeating, weight loss or anorexia, decreased energy and libido, or disturbance of the normal circadian and ultradian rhythms of some endocrine functions, activity, and body temperature (Spagnuolo et al., 2018; Tondo et al., 2003).

Several forms of depression can be distinguished, such as major depression, persistent depressive disorder, bipolar disorder, seasonal affective disorder (SAD), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, or atypical depression. Depression to maximum levels is a treatable mental illness. The factors which contribute to manage and treat the mainframe of depression are social, behavioural and physical support, psychotherapy, drug treatment - antidepressants- and miscellaneous like aerobic exercise; brain stimulation therapies; or electroconvulsive therapy. The medication prescribed for the pharmacological management and remedial treatment of all types of depression are classified as antidepressants (Khan et al., 2018; Linde et al., 2015). They are used to prevent from major depressive disorder and other conditions like generalized anxiety disorder (Jaeger et al., 2018), obsessive-compulsive disorder (OCD) (Fineberg et al., 2012), migraine, addiction, sleep disorders, dysthymia, dependence, eating disorders, bulimia nervosa, anorexia nervosa (Flament Spettigue, 2012), chronic pain, neuropathic pain (Lunn et al., 2014), or attention-deficit hyperactivity disorder (ADHD) (Linde et al., 2015).

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2. Depression

Depression are related from a biochemical point of view to metabolic dysfunction of monoamine neurotransmitters, concretely in noradrenaline (NA), serotonin (5-HT) and dopamine (DA) signalling leading to hypoactivity of these monoamines (Li et al., 2013a,b; Naughton et al., 2000). In fact, behavioural activity induced by antidepressant drugs is mediated by these neurotransmitters role. Indeed, brain-derived neurotrophic factors (BNDF) and *gamma*-aminobutyric acid (GABA) are described to be related to depressive disorders given that the 5-HT activity induces their production (Guan and Liu, 2016; Qiao et al., 2017). Monoamine oxidase (MOA) is a key enzyme responsible of the monoamine neurotransmitter breakdown; its activity has been revealed as a trait-dependent indicator of vulnerability to psychopathologies when is altered (Olsen et al., 2008). Corticotropin-releasing factor is the major physiological regulator of the hypothalamic-pituitary-adrenal (Farah et al., 2011) axis system, and acts within the central nervous system (CNS) so as to modulate behavioural, neuroendocrine and autonomic responses to environmental stimulation. In fact, it has been described that depressed patients have a damaged HPA axis function (Chang et al., 2016a; b).

3. Clinical antidepressant

Antidepressants can be divided according to mechanism of action, including serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), reversible inhibitors of monoamine oxidase A (RIMAs), NA reuptake inhibitors, tricyclic antidepressants (TCAs), tetracyclic antidepressants, tetracyclic analogues of mianserin, and specific serotonergic antidepressants, monoamine oxidase inhibitors (MAOIs), and melatonergic antidepressants. All of them are equally effective, but certain variation is being noticed in the type and severity of side effects (Garg and Ferguson, 2012; Gill and Wanogho, 1987; Lee et al., 2012; Michael Barbour et al., 2014).

Even though the therapeutic effectiveness of antidepressants available today the existing tools are frequently insufficient, with insufficient results in about one third of all treated patients (Aburawi et al., 2007; Alexander and Preskorn, 2014). The main reason for discontinuation of the antidepressant treatment is that the patient cannot tolerate their adverse effects such as serotonin toxicity (also known as serotonin syndrome) which is responsible for the induction of mania, restlessness, distress, instability, insomnia and confusion (Berrocoso et al., 2009; Casilla-Lennon et al., 2016). Other adverse effects include hypertensive crisis (Sathyanarayana Rao and 2009), spontaneous abortion (Nikfar et al., 2012), also symptoms of hypomania can be exacerbated (FB, 1997), or diminished sexual activities (Grant, 2012). Taking into account these part of the population, the development of new antidepressant drugs with a better efficacy and smaller amount of side effects is needed (Bhattamisra et al., 2008).

4. Herbal medication as an emerging source for depression treatment

Natural products and herbal medicines (ex. St. John's wort, saffron, *Rhodiola*, lavender, *Echium*, among others) are used for the treatment of mild to moderate depression. Preclinical studies are carried out in different animal models for emergence of new herbal products with better pharmacological and clinical characteristics (El-Alfy AT1 and Mastsumoto, 2012). Over the years, some new chemical entities with putative antidepressant profile have been revealed from the ethnopharmacological origins of herbal medicines and natural remedies (Dwyer et al., 2011; Sarris, 2011). The hypothetical reason for this switching over is related to the fact that drugs prescribed for neuropsychiatric disorders have more side effects than efficacy. Hence ayurveda has recently become a new research area of interest for the search of novel and better tolerated molecules from natural plant sources. Among the psychiatric disorders, individual reviewed herbal remedies have been classified as antidepressant, anxiolytic, antidementia, neuroleptic, or anti-substance abuse herbs (ZJ, 2004). Up till now, no serious complications have been recognized in the plant-based system of medicine. Different parts of plants are important but most active principles are present in leaves, fruit, flower, bark, seeds and root which vary in their concentration and extent of activity (Ramesh Patel and Pyush, 2012).

5. Flavonoids

According to a recent report, more than 6000 flavonoids are known with diverse pharmacological effects (Ali et al., 2017; Rauf et al., 2015b, 2015c, 2017; Xiao, 2017; Xiao et al., 2016). The neuroprotective like effect and antitumor action of isolated flavonoid have been recently reported (Nabavi et al., 2018; Rauf et al., 2015a; Xie et al., 2014). Flavonoids extracted from natural plant sources have been reported to possess antidepressant-like effect in many cell and animal studies (Khan et al., 2018; Lan et al., 2008). The antidepressant-like effect mechanism of flavonoids is well-defined in rats and it could be the reversal of monoamine neurotransmitter attenuations by 5-HT, NA and DA, and 5-hydroxyindoleacetic acid (5-HIAA), and most probably the regulation of the neurotransmitter receptor expression (Lu et al., 2010; Mannucci et al., 2012; Yan et al., 2016). Finally, it should be indicated that the effects on the CNS by flavonoids is one of their characteristics, but also possess a range of other biological activities (Athira et al., 2016; Cao et al., 2013; Chen et al., 2013; Kang et al., 2011). Overall, these compounds are found very stable (Xiao, 2018) and cardioprotective (Yu et al., 2017), however, some of them express acetylcholinesterase (Xu et al., 2016).

6. Structure-activity relationship between flavonoids and their antidepressant effect

Depending on their oxidative status and structural substituents, flavonoids are grouped into different classes. They can be biosynthesised via different pathways reforming in a C6-C3-C6, a skeleton consisting of two aromatic rings along with an oxygen-containing heterocyclic benzopyran ring. Labelled as the fused aromatic ring as A, the benzopyran ring adjacent to A as ring C, and the phenyl as ring B (Bruneton, 1999; Saaby et al., 2009). A double bond in ring C is present in flavonoids belonging to the flavones, flavonols and isoflavones groups, so the fused A-C ring is a planar system. The other flavonoids without a double bond in ring C have C2 and C3 placed on each side of the plane of the A ring, and also contain chiral centres at C2 and C3. In the environment, polymers are the structure in which flavonoids often occur; being dimers the most common form. The flavonoids are linked through C-C or C-O-C bonds (Bruneton, 1999). The two monoflavonoid-units of the biflavone may or may not be of the same type. In order to exert any effect on the CNS, flavonoids found in food or medicinal plants must pass the blood-brain barrier, and to achieve this goal they must be absorbed in the digestive tract, and transported by the circulatory system to the brain (Athira et al., 2016; Barreca et al., 2011).

Flavonoids possess a 2-phenyl-4*H*-chromen-4-one skeleton and have been defined as substances with a health-promoting potential. Flavonoids exist in mono-, di-, tri-, tetra- or polymeric form through C-C or C-O-C linkages. Flavonoids containing two or more units are pervasive natural products with maximum physiological activities, lesser toxicity and reduced side effects (Harborne and Williams, 2000). Two subclasses of flavonoids are the phenolic α, β-unsaturated ketones chalcones which contain a 1,3-diphenyl-2-en-1-one core, and flavanones, containing a 2-phenyl-2,3-dihydro-4*H*-chromen-4-one core (Kontogiorgis et al., 2008; Singh et al., 2014). Both subclasses have been extensively studied in relation to their antidepressant effects (Fig. 1) (Bukhari SN1, 2012; Katsori AM1, 2011; Yadav VR1, 2011).

The flavones like apigenin and luteolin and flavonols like quercetin

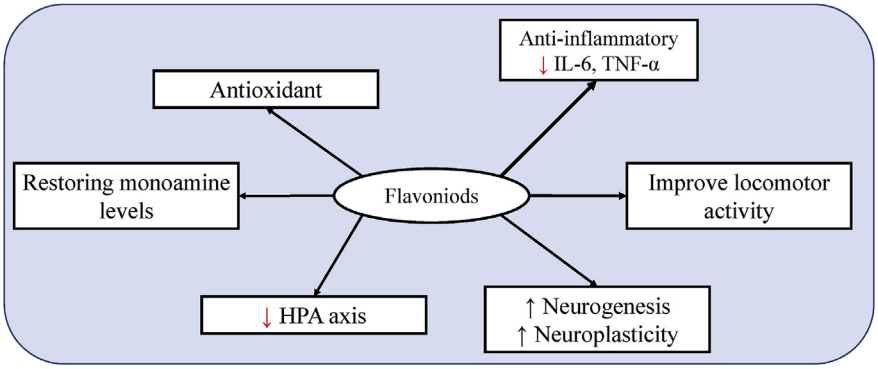


Fig. 1. Main anti-depressant mechanisms of action of flavonoids. IL-6: interleukin 6; TNF-α: tumour necrosis factor-*alpha*.

are capable to modulate the monoamine oxidase (MAO) activity and to show a potent antidepressant like effect due to its latent structure (Gong et al., 2014a; Han et al., 2007). The isoquercitrin and quercetin have been reported to interact with GABA receptors due its procurable structure like flavanones possessing a potential antidepressant effect (Wang, 2007). Flavonoids undergo derivatization such as glycosylation and glucuronidation that might induce or reduce the antidepressant effect at different levels, depending on the type of the sugar attached to them. Similarly, it has been described that quercetin, apigenin and luteolin, baicalin (containing a glucuronide group) (Han et al., 2007; Kashtriya et al., 2015; López-Rubalcava and Estrada-Camarena, 2016) and isorhamnetin possess antidepressant like effect mainly due to their structure.

Apigenin, fisetin, luteolin, kaempferol and quercetin are flavonoids with similar structure, being the number and location of hydroxy groups the difference between them; when these flavonoids were used in a structure-activity relationship study for antidepressant effects, the authors concluded that the position of hydroxy group(s) on the flavonoid A-ring influence antidepressant effects. Furthermore, compounds with hydroxy group(s) at 2,4-positions or the 4-position on the flavonoid A-ring showed antidepressant activities. Also, flavone derivatives possess antidepressant effects since flavone C-glucosides, both monosaccharides and disaccharides, exhibited better antidepressant activities (Guan and Y,-L 2016).

It has been described that the order of inhibitory potency against the MAO effect may be: flavone flavonol > flavone glycoside > flavanonol (Guan and Liu, 2016; Han et al., 2007; Vauzour et al., 2008). It has been described that an increasing number of hydroxyl groups or the presence of C-glycosides increased MAO inhibitory activity, that lowered the antidepressant-like activity by rising the hydrophilicity of these compounds, and thus, reducing their permeability across the blood-brain barrier (Guan and Liu, 2016).

7. Antidepressant effect of flavonoids

Numerous and different series of flavonoids isolated from natural plant sources have been reported in the literature in both *in vitro* and *in vivo* models (Table 1). Flavonoid compounds containing more than one pharmacophore have been described to have antidepressant-like effect (Bahramsoltani et al., 2015). Recent investigations suggest that dopaminergic mechanisms might be the responsible of the antidepressant-like effect of apigenin in the mouse brain (Yi et al., 2008) while luteolin might associate to the suppression of endoplasmic reticulum stress (Ishisaka et al., 2011). Other results performed in a rat model of chronic mild depression suggested that icariin inhibited the nod-like receptor protein 3-inflammasome/caspase-1/IL-1β axis and nuclear factor kappa B (NF-κB) signalling activation in hippocampus contributing to improve the depression deficits (Liu et al., 2015). Rutin displayed antidepressant-like activity by rising the 5-HT and NA availability in the synaptic cleft of experimental animals (Nöldner and, 2002).

Sloley et al. (2000) extracted kaempferol and quercetin, apigenin and chrysin from leaf of *Ginkgo biloba*, so as to study their neuroprotective effect in the brain of rats. The *in vitro* examination showed a pronounced inhibition of the monoamine oxidase-A (MAO-A) relating to antidepressant like effect. Other group extracted the flavonoid quercetin-3-O-apiosy1 (1 → 2)-rhamnosy1 (1 → 6) glucoside (CTN-986) from non-toxic cotton seed, which was documented to protect the nerve damage to PC12 nerve cells of rat adrenal medulla and relating this to the antidepressant effect (Li et al., 2000). Lee and colleagues worked on the leaves of *Melastoma candidum* D. Don. isolating four natural flavonoids, quercetin, isoquercitrin, quercitrin and rutin. The study revealed that all of them possessed both free radical scavenging and MAO-B inhibitory activities which is linked with preventing symptoms of anxiety and depression associated with neurodegenerative diseases (Lee et al., 2001).

Most studies have performed animal model of antidepressant action tests to assess the effects of flavonoids in animal depression models. A group of researchers extracted certain flavonoids like hyperoside, isoquercitrin, and quercetin-3-O-miquelianin along with rutin from *Hypericum perforatum*; they showed statistical effects in the forced swimming test (FST) in rats, consequently with the capability to treat the depression possessing almost the same potency as imipramine (Nöldner M, 2002). A Japanese group isolated apigenin from *Perilla frutescens* and studied their biochemical as well as behavioural effects on mice. From the study, it was evident that apigenin (12.5 and 25 mg/kg i.p.) mediated antidepressant like effect due to inhibition of monoamines by dopaminergic mechanism in brain of mouse (Nakazawa T, 2003). The flavonoids, flavan-3-ols (+)-catechin and (-)-epicatechin were isolated from the hook of *Uncaria rhynchophylla*. These flavonoids showed a remarkable protective action against neurodegenerative diseases by inhibition of MAO-B activity in rat brain, therefore managing the symptoms of anxiety and depression (Hou et al., 2005). It has been found in mouse that the active flavonoids, formononetin and kushenol F, from the roots of *Sophora flavescens* also demonstrating an inhibitory effect on brain MAO activity. The results of this cellular mechanism can be linked to its antidepressant like effects in mice (Hwang, 2005). Several flavonoids such as quercetin, quercitrin, kaempferol and kaempferol-3-orhamnopyranoside were isolated from an ethyl acetate extract of *Albizia julibrissin* which could produce an antidepressant-like effect in a despair mouse model of depression by remarkably reducing the immobility time (FST) (Li et al., 2006a,b). Pan et al. (2006) extracted icariin, liquiritin and isoliquiritin from *Epimedium brevicornum* which reduced the FST and tail suspension test (TST) immobility time showing a significant pharmacological treatment for the chronic mild stress-induced behavioural and neuroendocrinological alteration in rats. Additionally, another work described that *Hypericum monogynum* extracts including rutin, flavonides and isorhamnetin exhibited some significant antidepressant like effect due to catecholamine-*O*-methyltransferase (COMT)/MAO-inhibition (Paulke A, 2008). Chinese researchers isolated biacaline, from the dried root of *Scutellaria*

baicalensis. G. (Labiatae), which showed a remarkable decrease in the immobility time in TST and FST in murine models suggesting that baicalin has a specific antidepressant-like effect *in vivo* (Weili Zhu et al., 2008). Junko and co-workers isolated the isoflavone compounds genistein and daidzein from pomegranate, and the authors described a reduction in immobility time in the FST suggesting the clinical effectiveness on the state of depression in mice followed by an unknown mechanism (Mori-Okamoto et al., 2004). These results are in accordance with a Chinese team that isolated naringenin, a flavonoid from grapefruit juice, to test it for its antidepressant potential also resulting in a significant decrease in immobility time in TST (Yi et al., 2010, 2012). Other group of researchers isolated nobiletin, a flavonoid mostly found in citrus peels, and also observed a decreased in the immobility time of mice in both FST and TST suggesting the therapeutic potential of this dietary flavonoid for the treatment of depression (Yi et al., 2011). Amentoflavone was isolated from *Cnestis ferruginea* and significant reductions in mice in the interval of immobility in the FST and TST and the time spent in the open arms in the elevated plus maze were described. Therefore, it was concluded that amentoflavone possesses antidepressant as well as anxiolytic effect through proper cellular mechanism (Ishola et al., 2012b). Machado and collaborators isolated rutin from *Schinus molle* L. and found out that it could treat the depression in mice treated orally at different doses by reducing the time of immobility in TST which could be relevant in relation to the neurotransmitters SE, NA and DA in the central nervous system (Machado et al., 2007, 2008). A study done by Souza et al. (2013) showed that hesperidin (a flavan-on glycoside found in citrus fruits such as *Citrus aurantium*) reduced the immobility time in the FST and TST in mice by involving the binding to the serotonergic 5-HT (1A) receptor and conforming its antidepressant like effect. In this sense, the flavonoid hyperoside, isolated from *Apocynum venetum* leaves, in PC12 cells possibly exhibited antidepressant like activity possibly due to its cytoprotective action related to cyclic adenosine 3′,5′-monophosphate (cAMP) response element binding protein (CREB) elevation that has as a target the brain-derived neurotrophic factor (BDNF) (Zheng et al., 2012).

Astilbin, a flavonoid isolated from *H. perforatum*, has numerous pharmacological functions. By using the chronic unpredictable mild stress (CUMS) model of depression in mice the antidepressant-like effect of astilbin was studied. The authors observed reduced depressive-like behaviours by the flavonoid at several doses (10, 20 and 40 mg/kg i.p.) though the reduction in immobility time in the FST and TST, and an increase in the sucrose preference test (SPT); moreover, the treatment increased the 5-HT and DA levels in the frontal cortex inducing an upregulation of BDNF, indicating the mediation by the monoaminergic neurotransmitter pathways (Lv QQ1 et al., 2014).

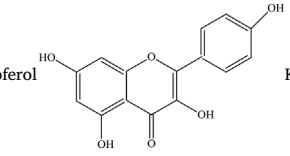
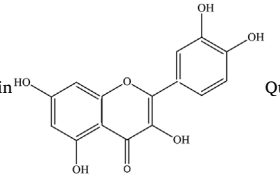
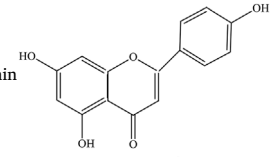
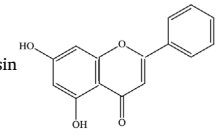
The antidepressant effects of flavonoids, chalcones, and flavanones have been widely and extensively reported (Bukhari and Jantan, 2012; Katsori and, 2011; Yadav et al., 2011). Isoliquiritin and liquiritin are chalcone and flavanone compounds with significant antidepressant-like effect, may throughout an increase in 5-HT and NA in the CNS (Wang et al., 2008). The antidepressant-like activity of hesperidin might be mediated by the L-arginine-NO-cGMP pathway inhibition through increasing BDNF and nerve growth factor (NGF) contents in the hippocampus (F. Donato et al., 2014). Another flavanone with potent antidepressant-like is naringenin that acts *via* the central noradrenergic and serotonergic systems (L.T. Yi et al., 2010). Except to naringenin, compounds with C-glucoside have been described to exhibit better antidepressant activity, suggesting the flavanone and chalcone maternal derivatives possess the antidepressant-like effect (Li-Ping Guan, 2016). In contrast, the flavonoid luteolin from *Cirsium japonicum* (CJ) was identified to have antidepressant like effects and its actions were possibly mediated through modulation of the $GABA_A$ receptor since no changes in NA were observed (de la Peña et al., 2014). In this sense, the potentiation of the $GABA_A$ receptor can enhance effects of the inhibitory neurotransmitter GABA contributing to the anti-depressive effects.

8. Anti-depression mechanism of flavonoids

8.1. Flavonoids' influences on biogenic amines

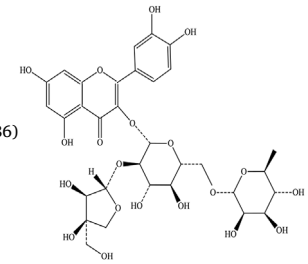
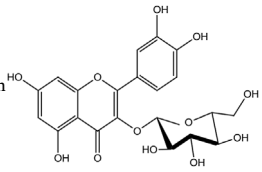
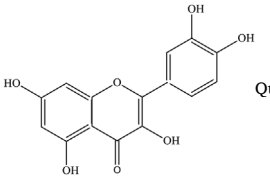
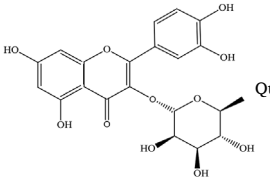
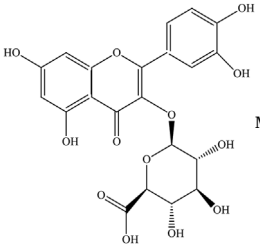
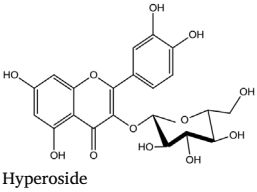
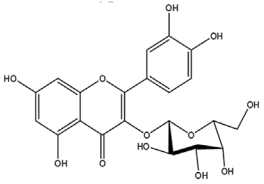
As it has been described above, in many of the flavonoids isolated from plants predominate their effect on monoamine neurotransmitters including 5-HT, NA and DA in both hypophysis cerebri and brainstem

Table 1
List of isolated flavonoids with antidepressant like effects.

Plant name	Flavonoids	Mechanism	Reference
Gingko biloba	kaempferol  Kaempferol	Inhibitors of MAO-A and MAO-B.	(Sloley et al., 2000)
	Quercetin  Quercetin		
	Apigenin 		
	chrysin 		

(*continued on next page*)

Table 1 (*continued*)

Plant name	Flavonoids	Mechanism	Reference
Non toxic cotton seed	Quercetin-3-O-apiosy1 (1 → 2)-rhamnosy1 (1 → 6) glucoside (CTN-986) 	Therefore, the antidepressant mechanism was considered to be related to the protection of nerve cells.[31]	(Li et al., 2000)
Melastoma candidum D Don (Melastomataceae)	Quercetin-3-O-apiosy1 (1 → 2)-rhamnosy1 (1 → 6) glucoside (CTN-986), isoquercetrin   Quercetin  Quercetrin	Inhibit MAO-B	(Lee et al., 2001)
Hypericum perforatum	Rutin Quercetin-3-O-miquelianin.  Miquelianin Isoquercitrin  Hyperoside 	Increase synthesis of serotonin or noradrenaline	(Nöldner M, 2002) (Nöldner and Schötz, 2002)

(*continued on next page*)

Table 1 (*continued*)

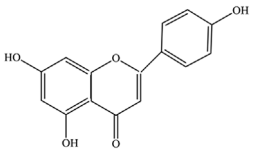
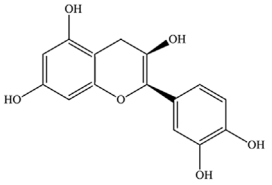
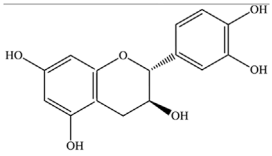
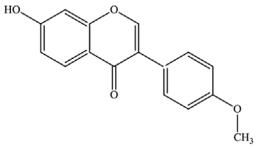
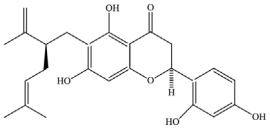
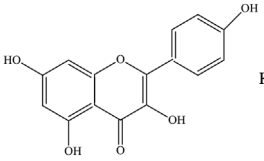
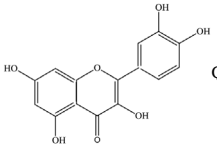
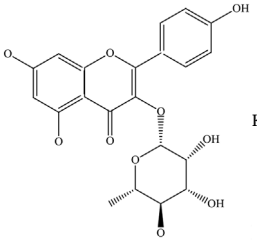
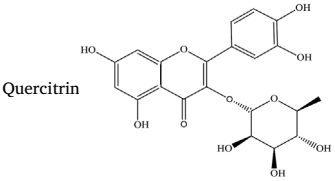
Plant name	Flavonoids	Mechanism	Reference
Perilla frutescens	Apigenin 	May be mediated by the dopaminergic mechanisms in the mouse brain. And inhibition of monoamines	(Nakazawa et al., 2003)
Uncaria rhynchophylla (Rubiaceae)	flavan-3-ols ( )-catechin and (-)-epicatechin  (-)- Epicatechin  (+)- Catechin	MAO-B	(Hou et al., 2005)
Sophora flavescens Ait. (Fabaceae)	Formononetin an isoflavone  Formononetin Flavanone kushenol F  Kushenol F	Monoamine oxidase inhibitory activity	(Hwang, 2005)
Albizia julibrissin	Kaempferol, quercetin, kaempferol-3-orhamnopyranoside  Kaempferol  Quercetin  Kaempferol-3-O-Rhamnopyranoside  Quercitrin	Decreased levels of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine in the brain	(Li et al., 2006a,b)

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Table 1 (*continued*)

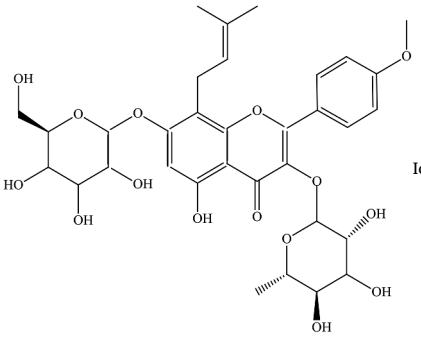
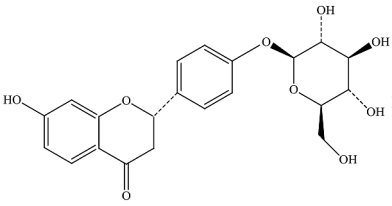
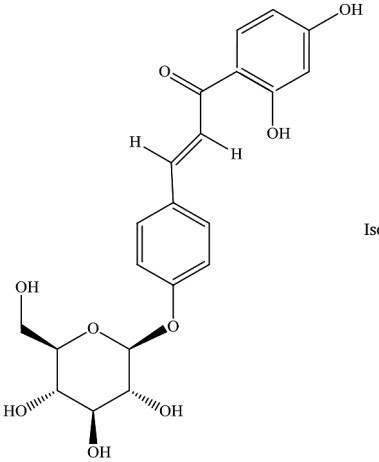
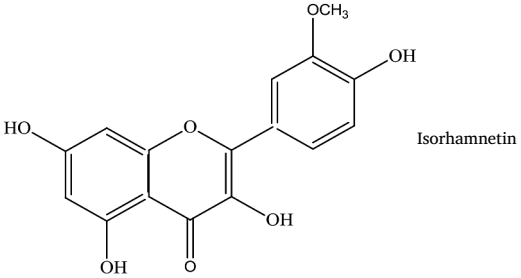
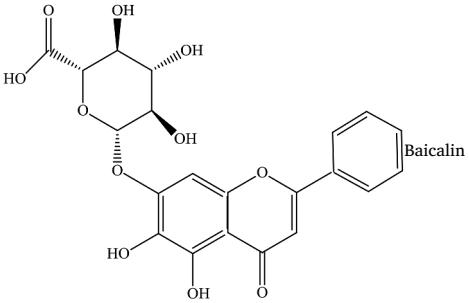
Plant name	Flavonoids	Mechanism	Reference
Epimedium brevicornum	Icariin  Icariin  Liquiritin  Isoliquiritin	By improving the abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis and hypothalamus-pituitary-thyroid (HPT) axis.	(Pan et al., 2007)
Hypericum monogynum	Isorhamnetin  Isorhamnetin	Decreased levels of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine in the brain	(Paulke et al., 2008)
Scutellaria baicalensis.	Baicalin  Baicalin	Monoamine oxidase (MAO A and B) inhibition	(Zhu et al., 2008)

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Table 1 (*continued*)

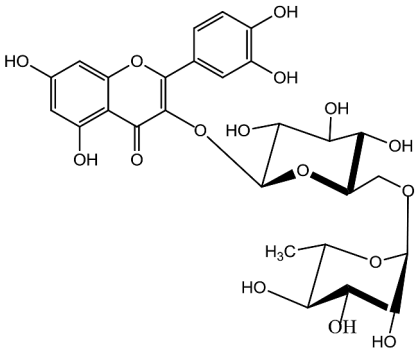
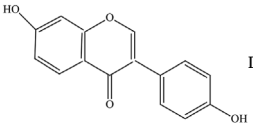
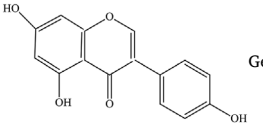
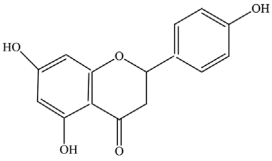
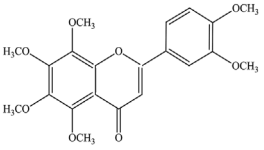
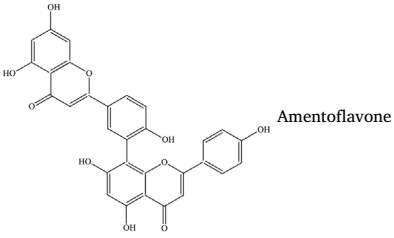
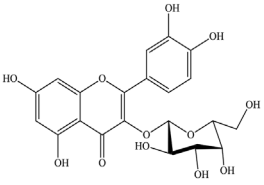
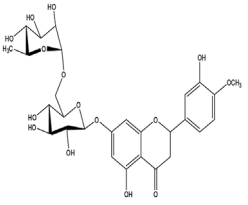
Plant name	Flavonoids	Mechanism	Reference
Schinus molle L.		Related to SE, NA, and DA.	(Machado et al., 2007)
Pomegranate extract	Genistein and daidzein  Daidzein  Genistein	Mechanism not studied yet	(Mori-Okamoto et al., 2004; Kageyama, akakibara, Zhou, Yoshioka, Ohsumi, Shimoi and Yokogoshi, 2010)
Grapefruit juice	Naringenin  Naringenin	Increased hippocampal 5-HT, NA and GR levels and reduced serum corticosterone levels in mice	(Yi et al., 2010)
Citrus peel	Nobiletin  Nobiletin	Mediated by an interaction with the serotonergic (5-HT_{1A} and 5-HT_2 receptors), noradrenergic (α_1-adrenoceptor) and dopaminergic (D_1 and D_2 receptors) systems.	(Yi et al., 2011)
Cnestis ferruginea	Amentoflavone as potent as imipramine (20 mg/kg),  Amentoflavone	It produces its antidepressant effect through interaction with 5-HT2 receptor and α1-, and α2-adrenoceptors while the anxiolytic effect involved the ionotropic GABA receptor.	(Ishola et al., 2012a, 2012b)
Apocynum venetum	hyperoside 	A cytoprotective action related to elevation the expression of BDNF and CREB through the signal pathway AC-cAMP-CREB.	(Zheng et al., 2012)
Citrus food *Citrus aurantium*	Hesperidin 	Dependent on an interaction with the serotonergic 5-HT (1A) receptors.	(Souza et al., 2013)

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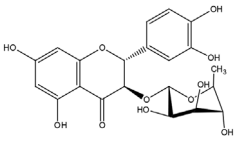
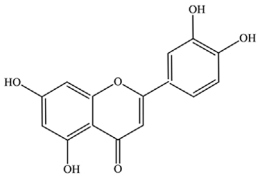
Table 1 (*continued*)

Plant name	Flavonoids	Mechanism	Reference
Hypericum perforatum	Astilbin 	Related to up-regulation of monoaminergic neurotransmitters (5-HT and DA) and activation of the BDNF signalling pathway.	(Lv QQ1 et al., 2014)
Cirsium japonicum (CJ)	 Luteolin	Mediated through potentiation of the GABAA receptor-Cl (-) ion channel complex.	(de la Peña et al., 2014)

(Fig. 2) (Zhang et al., 2001; Zhu et al., 2007). The antidepressant like effect of flavonoids is mainly related to the increase in the bioamine content, due to the restriction of the bioamines reuptake by synaptosomes and MAO activities. In fact, some researchers have investigated flavonoids with a similar structure to the one that synthetic MAO inhibitors have. Therefore, flavonoids can raise the content of 5-HT, DA and NA in neuron synaptosome and, as a consequence, reducing the clinical symptoms of depression.

8.2. Inhibiting the reabsorption of bioamines by synaptosomes

Other way of action of flavonoids isolated naturally is related to the possible 5-HT re-absorption prevention by limiting the number of 5-HT receptors and inhibiting the activity of catechinic acid-O-transmethylase with the assistance of synaptosomes; it seems that it may be critical for the antidepressant activity of some selected flavonoids (Carradori et al., 2016; Zhang et al., 2001). The effect in turn causes expression of brain monoamine neurotransmission (Gong et al., 2014b; Wasowski and Marder, 2012).

8.3. Flavonoids' influences on the neuroendocrine system

Taking into account the neuroendocrine system, the mechanistic impact of flavonoids concerning the antidepressant activity is on HPA axis, by enhancing the neurological function of 5-HT in brain as well as boosting up the action of adenylate cyclase (AC)-cAMP-CREB and its mediated neurotrophic factor with 5-HT receptors (Butterweck et al., 2000; Li et al., 2006a,b). The rise of some important factors, such as BDNF and phosphorylated CREB (pCREB) (Ser 133), is related to the hippocampal nerve synthesis (Fig. 3). Other well-modulated functional mechanisms connecting to antidepressant responses are signals transduction associated with hippocampal BDNF for a better neuroplasticity and neurotrophy (Bjorkholm and Monteggia, 2016; Knorr et al., 2017; Qiao et al., 2017; Zhao, 2007), raising hippocampal nerve synthesis and retrieving the BDNF and pCREB (Ser 133) expression (An et al., 2011). In chronically stressed rats, flavonoids affect HPA axis including the inhibition of stress hormones levels and the up-regulation of hippocampal glucocorticoid receptors (GRs) expression, and also by preventing PC12 nerve cell damage caused by a high concentrations of corticosterone and they can strongly bind with 5-HT1A (Fig. 4) (An et al., 2008; Patil et al., 2014). The increased sucrose intake is induced by chronic mild depression, and in blood it also alters the adrenocorticotropic (hormone)-releasing factor and cortisol levels; however, it has been described the restoration of interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) in the serum back to standard values after the action of flavonoids (Pan Y, 2006).

Many of flavonoids are inhibitors of triphosadenine and acetylcholine, others may restrain ATP and α-amino-3-OH-5-methane acid (V, 2003). By interacting with 5-HT_2 receptors, α_1, and α_2-adrenoceptors, flavonoids influence the antidepressant activity while the anxiolytic effect involved the ionotropic GABA receptor (Ishola et al., 2012a). One of the related mechanisms may involve restoration of cyclooxygenase-2 (COX-2) activity and a significant attenuation of chronic mild stress-induced prostaglandin E 2 (PGE 2) increases both in frontal cortex and hippocampus (Li et al., 2013a,b).

In addition, flavonoids significantly decreased the corticosterone and adrenocorticotropic hormone levels in plasma, and the mRNA expression of corticotropin-releasing factor in the hypothalamic region of rodents. Moreover, flavonoids were able to regulate in rats the expression of corticotropin-releasing factor (CRF) mRNA since they were capable to modulate DNA binding activities of the glucocorticoid receptor and cAMP and the phosphorylation of extracellular signal-regulated kinase 1/2 in the hypothalamic region (Kawabata, 2010).

9. Clinical prospects

There are numerous flavonoids derived from plants with outstanding preclinical effects as antidepressant and its related complications (Hritcu et al., 2017). Already, such compounds followed different singling pathways and demonstrated diverse mechanistic insights for their antidepressant like effects (Meyer et al., 2017; Zheng et al., 2013). Perez-Vizcaino and Fraga (2018) concluded in their review that the tremendous shift in the flavonoids research is due to their occurrence in fruits and vegetables (Perez-Vizcaino and Fraga, 2018). Similarly, recent epigenetic effects of flavonoids from common food staff further strengthen our belief in flavonoids research (Busch et al., 2015; Hua et al., 2016). In the light of strong preclinical potential, there is great need to evaluate their clinical profile.

Although there is a need to design clinical studies to evidence the potential anti-depressant effect of flavonoids, there are epidemiological evidences suggesting that a diet rich in flavonoids prevents the development of depression (Chang et al., 2016a; b; Khalid et al., 2016; Mihrshahi et al., 2015; Pase et al., 2013; Bouayed, 2010). In this sense, diverse authors investigated the anti-depressive effects of plant extracts rich in flavonoids. The most studied plant against mild-moderate depression is the extract of St. John's Wort (*Hypericum perforatum*). The results suggest that this plant could be effective for the treatment of mild-moderate depression when compared with placebo and has similar effects to pharmaceutical antidepressants (Mannel et al., 2010; Brattström, 2009; Kasper et al., 2006; Clement et al., 2006). However, not all results have been positive; in fact, St. John's Wort consumption could also lead significant side effects (Rapaport et al., 2011). In addition, other studies reported promising results against depression by using extracts of saffron (*Crocus sativus*), lavender (*Lavandula*

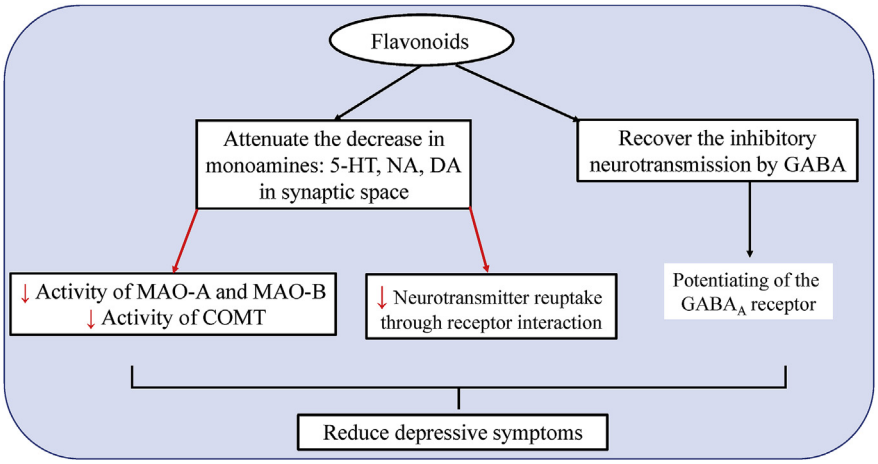


Fig. 2. Effects of flavonoids on altered neurotransmitters in depressive disorders. Flavonoids can attenuate the decrease in monoamines in the synaptic space and can recover the inhibitory neurotransmission by GABA. COMT: catecholamine-*O*-methyl-transferase; dopamine (DA); GABA: *gamma*-aminobutyric acid; MAO: monoamine oxidase; noradrenaline (NA) and serotonin (5-HT).

angustifolia), *Echium amoenum* and *Rhodiola rosea* (Dwyer et al., 2011). Unfortunately, except for saffron there is only one trial for each plant species being difficult to extract a conclusion about the potential therapeutic effects of flavonoids on depression. In the case of saffron, its consumption its consumption seems to be significantly more effective than placebo and equally as the pharmacological treatments (Shahmansouri et al., 2014; Moshiri et al., 2006; Noorbala et al., 2005). Moreover, some investigations can be found about effects of isoflavones against depressive symptoms in postmenopausal women. The consumption of red clover derived isoflavones has been evidenced to exert positive effects in reducing depressive and anxiety symptoms in postmenopausal women (Lipovac et al., 2010). A 2-years randomized trial also reported that genistein improved the health status, life satisfaction, and depressive symptoms in osteopenic postmenopausal women (Atteritano et al., 2014). However, not all results clearly evidenced the effectiveness of isoflavones. In one study investigating the treatment with soy isoflavones significant effects on the depressive symptoms of a predominantly affective nature were not reported (de Sousa-Muñoz and Filizola, 2009). A recent study investigated the effects of the consumption of a flavonoid-rich blueberry drink in children and young adults (Khalid et al., 2017). The acute consumption improved the mood in both groups measured by the Positive and Negative Affect Schedule-NOW (PANAS-NOW). Some of the plausible mechanisms which may explain these results are the inhibition of MAO and/or potentiating the effects of GABA via GABA$_A$ receptors by flavonoids.

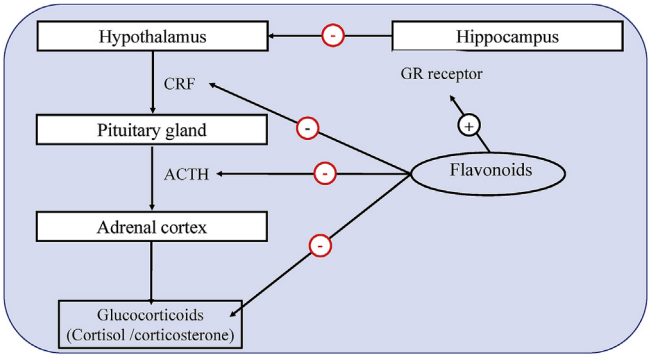


Fig. 4. Effects of flavonoids on the HTA axis. ACTH: adrenocorticotropic hormone; CRF: corticotropin-releasing factor; GR: glucocorticoid receptor; HPA: hypothalamic-pituitary-adrenal.

10. Toxicology

Food staff and related items are abundant in flavonoid contents and in various experiments, they are found to be safe and free from side effects up to the maximum possible dose (Peng et al., 2016). However, to avoid any possible toxicity, in case of flavonoids, the recommended daily allowance is suggested to be 250-400 mg/d (Peluso and Palmery, 2015). Additionally, the protective role of different flavonoids is found to be varied in different disease (Woo and Kim, 2013). Similarly, fisetin, a flavonoid, caused down-stream regulation of progesterone production

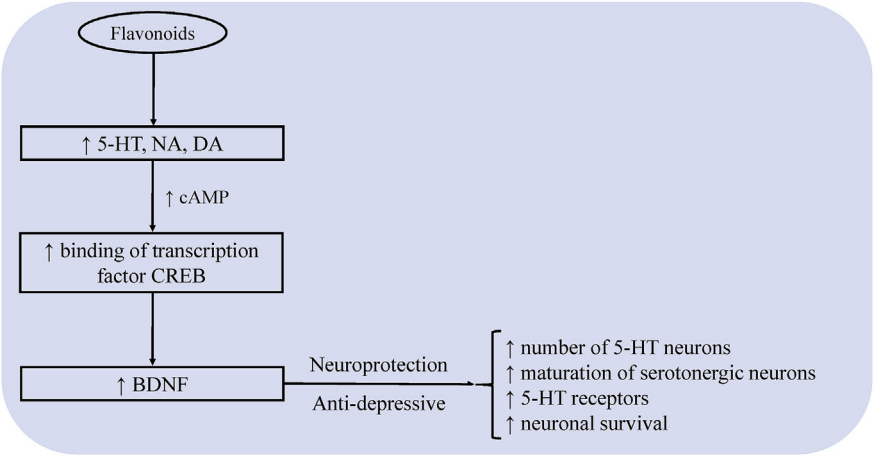


Fig. 3. Flavonoids can exert neuroprotective and anti-depressant effects by up-regulating the BDNF pathway. BDNF: brain-derived neurotrophic factor; CREB: cyclic adenosine 3′,5′-monophosphate (cAMP) response element binding protein (CREB).

in ovarian granulosa cells and thus might have an aggravating action (Bujnakova Mlynarcikova and Scsukova, 2018). This revealed that the safety of one component may not assume for other, rather must be verified in related experiments.

11. Conclusions

Depression is addressed with different treatments which have been effective until a certain degree; albeit they have shown heterogeneity of clinical response, present different side effects and appear to possess several targets. This situation leads to the need for finding new strategies and natural products, such as flavonoids, are being studied with this purpose. In fact, nerve cell lines and animal models have revealed promising results in order to treat depression, and the researchers have pointed out that the mechanisms implicated in the process involved the serotonergic, noradrenergic and dopaminergic systems. Among them, a decrease in the monoamine oxidase –both type A and B- and the up-regulation of BDNF and CREB are one of the main factors related to neuroprotection, although the inhibition of the reuptake of biogenic amines may are also related to. Reaching a normal HPA axis activity is also related to the improvement of the depression since it is increased in this pathology. On the other hand, works in humans are scarce. Clinical trials are needed since only few studies have been addressed, these studies are based in psychological tests in human and no biochemical data are still available from these patients. More research to know the mechanistic pathways in humans are essential for a better understanding of the action of flavonoids on pathways in order to counteract depression symptoms.

Conflict of interst

All authors declare that they have no conflicts of interest.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.04.052.

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