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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