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Review article

Antidepressant-like effects and mechanisms of flavonoids and related analogues

Li-Ping Guan*, Bing-Yu Liu

Food and Pharmacy College, Zhejiang Ocean University and Zhejiang Provincial Engineering Technology Research Center of Marine Biomedical Products, Zhejiang, Zhoushan, 316022, PR China

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ABSTRACT

Flavonoids, possessing a basic phenylbenzopyrone core, are important components of the human diet, and are found in many medicinal plants. Flavonoids include chalcones, flavanones and their derivatives. Synthetic and natural isolated flavonoids display an enormous number of biological activities such as antitumor, antiplatelet, anti-malarial, anti-inflammatory, antidepressant and anticonvulsant properties. This review article focuses on the antidepressant-like effect, structure–activity relationship and mechanism of action of total flavonoid extracts isolation from natural sources, flavonoid compounds and their related analogues.

Contents

1. Introduction

Flavonoids possess a 2-phenyl-4*H*-chromen-4-one skeleton, and are potentially health-promoting substances (Fig. 1). 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 ubiquitous natural products with wide physiological activities, low toxicity and few side effects [1]. Flavonoids are phytochemicals found in a variety of fruits and vegetables and confer color, flavor, and aroma, as well as nutritional and health benefits [2–4]. Many flavonoids possess antioxidant, anti-inflammatory and antidepressant activity in animal studies [5–11].

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 (Fig. 1). A large number of naturally occurring and structurally modified flavonoids, chalcones, and flavanones have been chemically synthesized, with numerous publication highlighting the synthesis and medicinal significance of these compounds [12–16]. The antidepressant effects of flavonoids, chalcones, and flavanones have caused widespread interest and have been widely studied [17–24]. This paper is a mini-review of

* Corresponding author.
E-mail address: glp730@163.com (L.-P. Guan).

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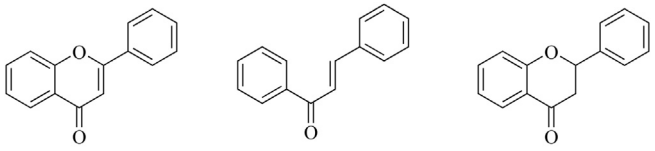

Fig. 1. Structures of flavonoids, chalcones and flavanones.

the antidepressant-like activity of natural and synthetic flavonoid, chalcone and flavanone compounds that have been published in the last fifteen years (2000–2015). The structure–activity relationship (SAR) and mechanism of action of these compounds are also discussed.

2. Structure-activity relationship and antidepressant effects

Depression is one of the most prevalent psychiatric disorders, and is characterized by a decrease in an individual's ability to experience pleasure. Symptoms of depression include lowered pleasure, mood and interest. Depression is a chronic and disabling mental illness that causes high morbidity and mortality [25–27]. The World Health Organization (WHO) estimates about 350 million people suffer from depression, and predicts that by 2020 the disorder will be the second leading cause of disability worldwide [28–30]. The main biochemical causes of depression are metabolic disorders of monoamine neurotransmitters that are involved in noradrenaline (NE), serotonin (5-HT), and dopamine (DA) signaling [31,32]. These neurotransmitters play important roles in mediating behavioral activity induced by antidepressant drugs. Brain-derived neurotrophic factors (BNDF) and *gamma*-aminobutyric acid (GABA) are believed to be associated with depressive disorders [33,34]. Monoamine oxidase (MOA) is a key enzyme that is related to the metabolism of these neurotransmitters. Reduced or elevated MOA activity has been indicated as a trait-dependent indicator of vulnerability to psychopathologies [35]. The function of the hypothalamic-pituitary-adrenal (HPA) axis was damaged in many depressed patients [36]. Corticotropin-releasing factor, the major physiological regulator of the HPA axis system, acts within the central nervous system (CNS) to modulate a lot of behavioral, neuroendocrine and autonomic responses to environmental stimulation [37].

Although there are many effective antidepressants available today the current armamentarium is often inadequate, with unsatisfactory results in about one third of all subjects treated [38,39]. The discovery of new antidepressant drugs with better efficacy and fewer side effects is necessary. The antidepressant-like effect of natural and synthetic flavonoid, chalcone, and flavanone derivatives are discussed in this section.

2.1. Extracted flavonoids

Many flavonoids extracted from plants have been reported to possess antidepressant-like effect in animal studies. The mechanism of the antidepressant-like effect of these flavonoids in rats is reversal of monoamine neurotransmitter attenuations by 5-HT, NE and DA and 5-Hydroxyindoleacetic acid (5-HIAA), and regulation of the gene for neurotransmitter receptor expression [40–45].

A flavonoid fraction obtained from a crude extract of *Hypericum perforatum* (St. John's Wort) significantly induced the immobility time in forced swimming tests (FST), and showed antidepressant-like effect in mice. The fraction was further separated using multi-layer coil counter-current chromatography (MLCCC) and high performance liquid chromatography (HPLC) and composed mainly of hyperoside, isoquercitrin, miquelianin, quercetin, the aglycones quercitrin and astilbin [46,47]. Butterweck et al. reported that the major flavonoids (hyperoside and isoquercitrin) extracted from the leaves of *Apocynum venetum L.* (Apocynaceae) markedly shortened the immobility time of male rats at doses of 30, 60, and 125 mg/kg, respectively, in a FST, suggesting a possible antidepressant-like activity. The effects were comparable to that of the tricyclic antidepressant imipramine (20 mg/kg). Neither the *Apocynum* extract nor imipramine produced any overt behavioral changes or motor dysfunction in the open field test (OFT) [48].

Hypericum perforatum is considered an effective alternative to the synthetic antidepressants for the treatment of mild-to-moderate depression. Calapai et al. [49] used HPLC to study neurotransmitter 5-HT, NE and DA contents in different brain regions (diencephalon, cortex, and brainstem) of male Sprague–Dawley rats after administration of *hypericum* flavonoid extracts by the FST. The *Hypericum* extract increased 5-HT, NE, and DA levels and reduced the immobility time with acute oral administration (*per os, p.o.*) (50, 250 and 500 mg/kg). The antidepressant-like effect is probably mediated by serotonergic, noradrenergic, and dopaminergic system activation.

Dhingra et al. [50] investigated the antidepressant-like activity of an aqueous extract of *Glycyrrhiza glabra L.* (liquorice) using the FST and the tail suspension test (TST) in mice. The extract of *G. glabra* was administered for 7 successive days at doses of 75, 150, and 300 mg/kg (*o.p.*), respectively, in Swiss young male albino mice. The 150-mg/kg dose significantly decreased the immobility time in both the FST and TST. The liquorice extract also reversed reserpine-induced extension of the immobility period. Alpha-adrenergic blocker prazosin (alpha1-adrenoceptor antagonist) and antipsychotic sulpiride significantly attenuated the extract-induced antidepressant-like activity in the TST. *p*-Chlorophenylalanine (PCPA) (inhibitor of serotonin synthesis), an inhibitor of 5-HT biosynthesis, did not invert the antidepressant-like activity of the liquorice extract. This suggests that the antidepressant-like activity of liquorice extract may be mediated by increasing brain DA and NE, and not by increasing 5-HT.

Xiaobuxin-Tang (XBXT) is a traditional Chinese herbal decoction. Zhang et al. [51] found that the ethanolic extract of XBXT significantly decreased the immobility time in the TST and FST in mice and rats [52]. Acute and sub-chronic treatments with the total flavonoids (XBXT-2) extracted from XBXT exerted excellent antidepressant-like effect in animal depression, behavioral despair, and learned helplessness models in rats. XBXT-2 may contain the most active antidepressant components of XBXT [53]. An et al. [54] demonstrated that administration of XBXT-2 (25 and 50 mg/kg, *p.o.*) reversed the behavioral alterations and serotonergic dysfunctions in chronic mild stress (CMS) rats, suggesting that XBXT-2 exerted significant antidepressant-like effect, and that serotonergic activation might be involved in XBXT-2 effect. An et al. further demonstrated that XBXT-2 possesses excellent antidepressant-like effect in multiple animal models of depression. Morphologic and functional regulation in the hippocampus, including up-regulation of hippocampal neurogenesis and neurotrophins expression, may be involved in its antidepressant-like efficacy of XBXT-2.

Messaoudi et al. [55] reported antidepressant-like activity of cocoa polyphenolic extract, a complex mixture prepared from non-roasted cocoa beans including high contents of flavonoids using the FST in rats. Their studies showed that cocoa polyphenolic extract significantly lessened the duration of immobility at doses of 24 and 48 mg/kg for 14 days, respectively. No change in motor dysfunction was observed with two doses in OFT. Locomotor effect tests confirmed the assumption that the antidepressant-like effect of cocoa polyphenolic extract is specific after subchronic treatment in