The Anxiolytic- and Antidepressant-like Effects of Flavonoid Chrysin

Subjects: Integrative & Complementary Medicine

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Flavonoids are polyphenolic compounds that are present in plants. They produce pharmacological actions in the peripheral and the central nervous system (CNS). They can cross the blood–brain barrier and interact with several neurotransmission systems and, thereby activating signaling pathways in specific brain structures involved in the physiopathology of anxiety and depression disorders. In particular, the flavonoid chrysin (5,7-dihydroxyflavone) has been studied for its antioxidant properties; however, its neuropharmacological effects in specific brain structures involved in the physiopathology of several neuropsychiatric disorders, such as anxiety and depression, need to be studied.

Animal model antidepressant anxiolytic BDNF chrysin flavonoid GABAA receptor natural medicine neuropharmacology GABAergic system

1. Generalities of the Flavonoid Chrysin

Chrysin (**Figure 1**) has a backbone structure that consists of a fused A and C rings, and a phenyl B ring, which is attached to the second position of ring C and shares the basic structure of the flavones, with an additional hydroxyl group at the fifth and seventh positions of the A ring. The potential of chrysin to act as a free radical scavenger has been attributed to the presence of these hydroxyl groups [1][2], and it has been suggested that these functional groups represent the main site of action of this flavonoid to produce a great variety of pharmacological activities and therapeutic effects. It has the potential to be used as an alternative in the treatment of metabolic, cardiovascular, and neuropsychiatric disorders [3]. In addition, the presence of hydroxyl groups in the backbone of chrysin has been associated with its anxiolytic-like effects [4]. Chrysin, but not the flavone backbone, decreases anxiety-like behavior in rats and zebrafish, suggesting that the presence of hydroxyl groups in its basic structure is indispensable for producing anxiolytic-like effects in pre-clinical research [4].

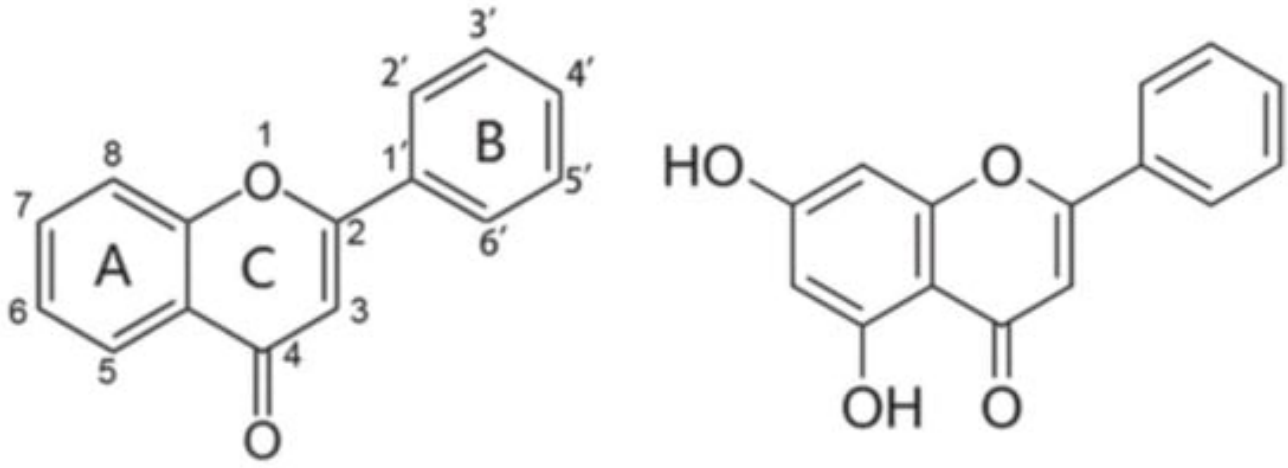

Figure 1. Basic structure of flavones showing fused A and C rings, and phenyl B rings with corresponding numbering system (**left figure**). Structure of the flavonoid chrysin, 5,7-dihydroxyflavone (**right figure**).

Chrysin, either isolated from plants like *Passiflora coerulea*, *Passiflora incarnata*, and *Matricaria chamomilla*, or even as a synthetic drug, produces anxiolytic- and antidepressant-like effects. These effects involve several activations of neurotransmission systems and signaling pathways, including the serotonergic and GABAergic systems, and the activation of neurotrophic factors, such as BDNF and NGF. It is likely that the activation of anti-inflammatory and antioxidant signaling pathways may also be involved in these effects. Although these effects have been principally evaluated in pre-clinical research [5][6][7][8][9][10][11], they show the potential therapeutic use of chrysin for anxiety, depression, and other neuropsychiatric disorders.

2. Anxiolytic-like Effects of Flavonoid Chrysin

In 1994, Wolfman et al. reported an anxiolytic-like effect of chrysin in mice. A single dose of chrysin at 1 mg/kg significantly increased the time spent in open arms of the EPM [9]. In the light/dark box (LDB), increased time was spent in the illuminated compartment [7], and in both cases the effects were similar to that produced by diazepam. These behavioral effects are considered to be associated with anxiolytic-like effects in pre-clinical research. Chrysin, but not diazepam, is devoid of motor effects related to sedation [9] and this may represent the advantage of chrysin over benzodiazepines, such as diazepam, in the treatment of anxiety disorders [12]. Interestingly, in male Sprague Dawley rats, the anxiolytic-like effects of chrysin at 1 and 2 mg/kg in LDB were blocked by a previous administration of flumazenil [7][13], an antagonist of the benzodiazepine binding site in the $GABA_A$ receptor. Additionally, acute administration of chrysin (1 mg/kg) produced anxiolytic-like effects in male Wistar rats [14] and CD-1 male mice [15] evaluated in the EPM. Similarly, anxiolytic-like effects of chrysin in mammals (mice and rats) have also been reported in non-mammalian organisms (zebrafish). Chrysin at 1 mg/kg decreased anxiety-like behavior in rats and zebrafish, similar to diazepam [4]; however, treatment with a flavone backbone at 1 mg/kg was devoid of anxiolytic-like effects in both rats and zebrafish, suggesting that the presence of hydroxyl groups in its basic structure could be indispensable to produce anxiolytic-like effects [4].

Anxiety symptoms in women are associated with a reduction in steroid hormones, such as estradiol and progesterone, and its reduced metabolite allopregnanolone in the peripheral and CNS, which may occur pre-menstruation, post-partum, and during the transition to menopause stage [16][17]. These steroid hormones may modulate several neurotransmission systems, such as the serotoninergic, noradrenergic, dopaminergic, and GABAergic [18]; therefore, some of these hormones have been proposed as novel groups of anxiolytic drugs for treating particular anxiety and depression disorders associated with reduced concentrations of steroid hormones [19]. It has recently been proposed that the flavonoid chrysin mimics some of the pharmacological effects of neurosteroids in female rats [20]. Anxiety-like behaviors in female rats significantly increase during the metestrus–diestrus phase of the ovarian cycle, which is associated with a low concentration of steroid hormones [21]; this phase is considered an equivalent of the premenstrual period in women [22]. Interestingly, chrysin at 2 mg/kg, similar to diazepam at 2 mg/kg, prevents anxiety-like behavior that naturally occurs during the metestrus–diestrus phase in female rats evaluated in the EPM and LDB. This effect can be blocked by a previous injection of picrotoxin [23]. In support, microinjection of chrysin at 0.5 µg in the dorsal HP prevented anxiety-like behavior that naturally occurs during diestrus, which was blocked by previous injection of picrotoxin, bicuculline, and flumazenil, indicating that the GABA/benzodiazepine receptor complex in the dorsal HP mediates the anxiolytic-like effects of this flavonoid [24]. Interestingly, this same effect on anxiety-like behavior during diestrus was prevented by microinjection of neurosteroid allopregnanolone at 0.5 µg into the dorsal HP, which was blocked by picrotoxin, bicuculline, and flumazenil in the EPM [24]. In contrast, in a surgical menopause model in rats characterized by high anxiety-like behavior associated with a permanent reduction of steroid hormones, chrysin at 2 and 4 mg/kg and diazepam at 1 mg/kg, reversed this anxiety-like behavior, which was blocked by a previous injection of picrotoxin [11]. The fact that picrotoxin, bicuculline, and flumazenil prevented the anxiolytic-like effect of different doses of chrysin supports the idea that its pharmacological effects are established on the GABA/benzodiazepine receptor complex, as occurs with clinically effective GABAergic anxiolytic drugs and several neurosteroids, such as allopregnanolone [25], but does not produce the typical sedative effects of benzodiazepines [9]. However, the researchers cannot discard the possibility of other neurotransmitter systems' participation and the anti-inflammatory and antioxidant effects in different regions of the brain due to the anxiolytic-like effects of chrysin (**Figure 2**). Specific studies are required to support or discard this possibility.

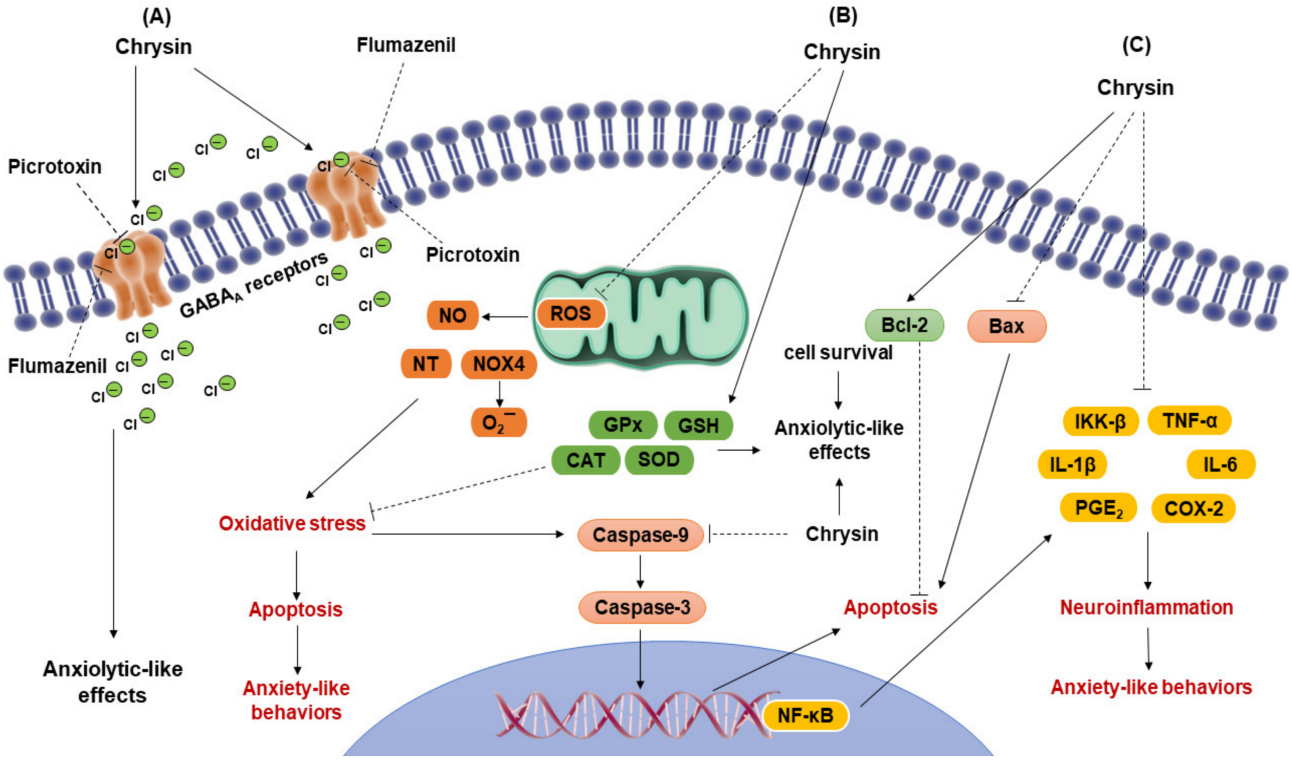

Figure 2. Mechanism of action of the flavonoid chrysin potentially involved in its anxiolytic-like effects. (**A**) It has been confirmed that chrysin produces its anxiolytic-like effect through its action on the $GABA_A$/benzodiazepine receptor complex producing configurational changes in the receptor and regulating the opening of the Cl^- ion channel [5][7][9][26][27], which may produce inhibitory effects in the GABAergic system associated with its anxiolytic-like effects. These effects can be blocked by specific antagonists of the $GABA_A$ receptor, such as picrotoxin, bicuculline, and flumazenil [5]. (**B**) Probably, antioxidant effects of chrysin could be involved in its anxiolytic-like effects. Chrysin significantly reduces ROS by inhibiting the production of NO, NT, and NOX4 [28]. These effects reduce the oxidative stress and reduces the neuronal damage. Additionally, chrysin reduces the activity of Bax, caspase-9, and caspase-3, while increasing the production of Bcl-2, thereby reducing the damage of DNA and inhibiting apoptotic processes [29][30], which reduces the neuronal death. (**C**) Additionally, the anti-inflammatory effects of chrysin could contribute to its anxiolytic-like effects, considering that it may reduce the inflammatory response by inhibiting the signaling pathway NF-κB/IKK-β [31][32]. Chrysin may attenuate the expression of NF-κB that participates as transcriptional factors at nuclear level, binding to genes that induce neuro-inflammation process. Chrysin also inhibits the production of pro-inflammatory cytokines, such as IL-1β and IL-6, in addition to suppressing the production of proinflammatory mediators, such as TNF-α, PGE_2 and COX-2 [31][32][33]. These effects could reduce neuro-inflammation associated with the anxiety-like behavior. ROS = reactive oxygen species; NO = nitric oxide; NT = nitrotyrosine; NOX4 = NADPH oxidase; $O2^-$ = superoxide; Green circles = chlorine ions; SOD = superoxide dismutase; GSH = reduced glutathione; CAT = catalase; GPx = glutathione peroxidase; Bcl-2 = anti-apoptotic protein of the subfamily Bcl-2; Bax = pro-apoptotic protein of the subfamily Bax; NF-κB = nuclear factor kappa B; IKK-β = inhibitor of nuclear factor kappa-B; TNF-α = tumor necrosis factor-α; IL-1β = interleukin-1β; IL-6 = interleukin-6; PGE2 = prostaglandins E2; COX-2 = cycloxygenase-2. (Figure was prepared by the authors).

3. Antidepressant-like Effects of Flavonoid Chrysin

Few studies have explored the antidepressant-like effects of chrysin; however, their results are promising. Filho et al. [8] reported that chrysin at 5 and 20 mg/kg for 28 days increased sucrose consumption and decreased immobility in the tail suspension test (TST) in female mice C57B/6J exposed to CUMS, which is considered to have antidepressant-like effects in pre-clinical research. This effect was also associated with an increase in serotonin, BDNF, and NGF levels, and decreased pro-inflammatory levels of cytokines, such as TNF-α, IFN-γ, IL-1β, and IL-6 in the HP and PFC of C57B/6J mice [8][34]. Additionally, chrysin at 20 mg/kg for 14 days produced an antidepressant-like effect in the FST in male mice C57B/6J subjected to depression induced by olfactory bulbectomy. This effect was associated with decreased pro-inflammatory cytokines (i.e., TNF-α, IFN-γ, IL-1β, IL-6), kynurenine (KYN, a metabolite resulting from serotonin degradation), and indolamine-2, 3-dyoxigenase (IDO, enzyme responsible for serotonin metabolism) activity, besides producing an increase in BDNF and serotonin levels in HP [10]. Interestingly, chrysin at 1, 5, and 10 mg/kg for 28 days produced antidepressant-like effects in the FST in male Wistar rats [35]. In addition, chrysin at 1 and 5 mg/kg for 28 days significantly reduced 5-HT_{1A} receptor expression in the raphe nucleus and increased it in HP, whereas 5-HT_{2A} receptor expression was increased in HP [35]. These effects were similar to those produced by the antidepressant fluoxetine at 1 mg/kg for 28 days. In another study, chrysin at 20 mg/kg for 28 days produced antidepressant-like effects in the TST and FST in female C57BL/6 mice exposed to a depression model induced by hypothyroidism, which was associated with increased serotonin and dopamine levels in the HP [36].

As previously mentioned, a reduced concentration of ovarian hormones in women during their transition to menopause, increases the risk of developing anxiety and depression symptoms [37]. Interestingly, using a surgical menopause model in Wistar rats, it was reported that chrysin at 1 mg/kg reversed depression-like behavior in the FST; this effect was similar to that produced by neurosteroids progesterone at 1 mg/kg and allopregnanolone at 1 mg/kg [20]. The effects of chrysin and neurosteroids were blocked by the previous administration of bicuculline, a selective competitive antagonist of the binding site of γ-aminobutyric acid in the $GABA_A$ receptor, which supports the idea that activation of the GABAergic system participates in the antidepressant-like effect of chrysin, as has been reported with neurosteroids [38].

Based on the results described above, the researchers suggest that the mechanism of action underlying the antidepressant-like effect of chrysin involves multiple neurochemical processes, such as the activation of neurotransmitter systems, anti-inflammatory and antioxidant processes, and the activation of neurotrophic factors (**Figure 3**); however, further exploration is required to improve people's understanding of these mechanisms underlying the antidepressant-like effects of chrysin, and to explore its effects in controlled clinical trials.

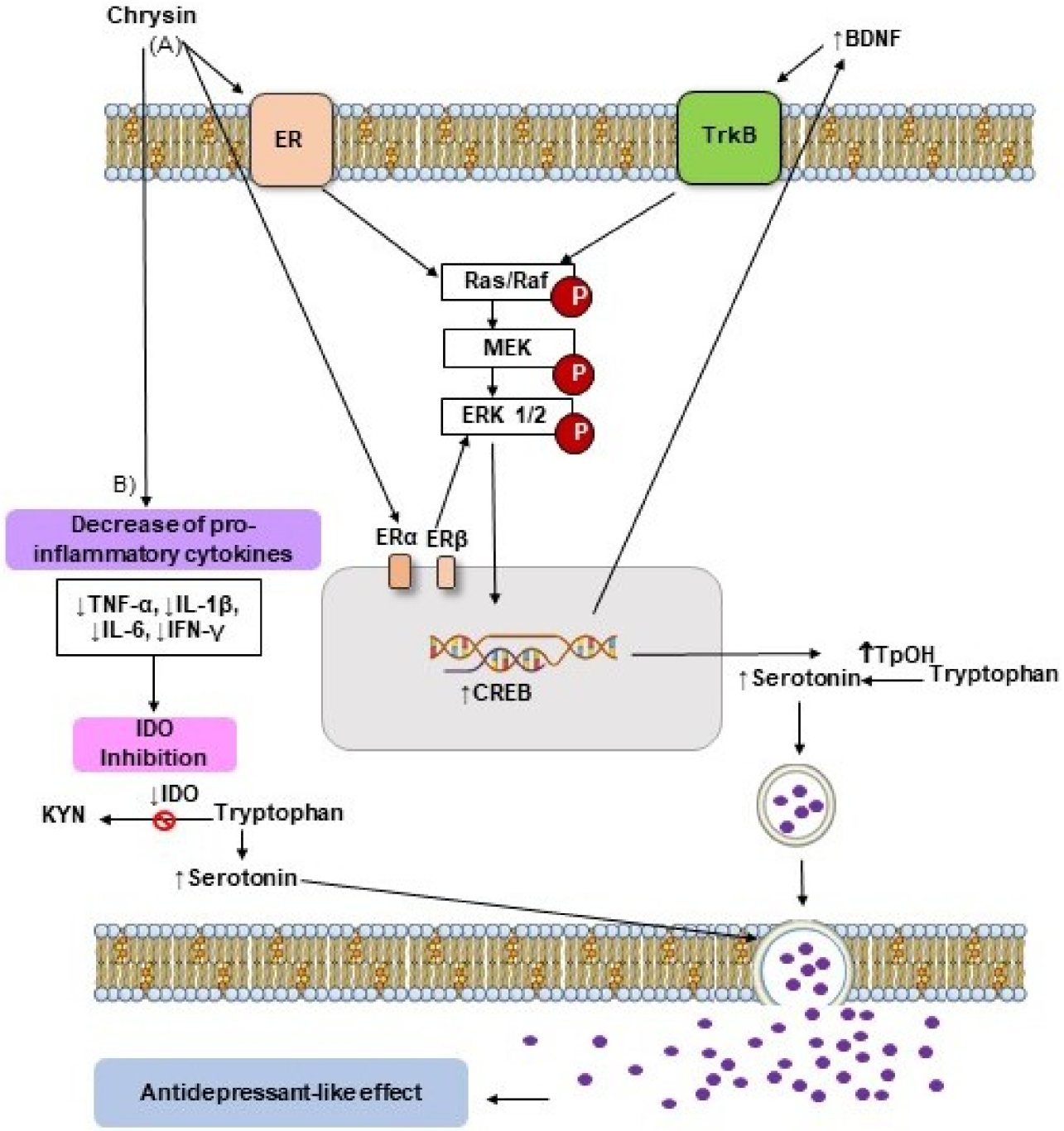

Figure 3. Possible mechanisms of action involved in the antidepressant-like effect of chrysin. (**A**) The flavonoid chrysin can modulate ERα and ERβ of membrane, which triggers the MAPK/ERK1/2 signaling pathway involved in phosphorylation and subsequent CREB activation (↑CREB), which promotes the increase of BDNF levels (↑BDNF) [1][34][39][40], which can further activate the MAPK/ERK1/2 signaling by the TrkB interaction [41]. The above-mentioned pathway also promotes an increase of TpOH expression (↑TpOH) and serotonin levels (↑Serotonin) resulting in the antidepressant-like effect [10][36]. (**B**) Furthermore, chrysin can decrease the pro-inflammatory cytokine levels (↓TNF-α, ↓IL-1β, ↓IL-6, ↓IFN-γ), which inhibits IDO activity (↓IDO) improving serotonergic neurotransmission and producing its antidepressant-like effect [10]. ER = estrogen receptor; MAPK = mitogen-activated-protein-kinases; CREB = cAMP response element binding; BDNF = brain derived neurotrophic factor; TrkB = tropomyosinreceptor kinase B; TpOH = tryptophan-hydroxylase; TNF-α = tumor necrosis factor-α; IL-1β =

interleukin 1 beta; IL-6 = interleukin 6; IFN-γ = interferon gamma; IDO = indoleamine 2,3-dioxygenase; ERK1/2 = extracellular signal-regulated kinase 1 and 2; KYN = kynurenine. (Figure was prepared by the authors).

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