



Bioactive Components for Depression: Naringin, Caffeine, Probiotics, Saffron and Lavender May Exert Antidepressant Effects Through Inflammation Modulation

Ahmad Shamabadi^{1,2} and Shahin Akhondzadeh^{2*}

1. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

2. Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran

Depression is one of the most prevalent psychiatric illnesses, leading to increased functional disability and mortality. Current pharmacotherapy is moderately effective, with response rates and remission rates reported at 50% and 15-40% following the first trial with conventional drugs, respectively, and electroconvulsive therapy is beneficial for only half of the refractory patients. A more accurate understanding of pathophysiology and the use of complementary therapies to overcome resistance to treatment have been suggested (1). After serotonergic and then glutamatergic systems, new research in the pathophysiology of depression has turned to the inflammatory mechanism. In this mechanism, cytokines disrupt tryptophan, Brain-Derived Neurotrophic Factor (BDNF), cAMP Response Element-Binding protein (CREB), and tropomyosin receptor kinase B (TrkB) levels balance (2). This mechanism is briefly described in figure 1. Celecoxib, simvastatin, pioglitazone, and dexamethasone are the medications that have had both antidepressant and anti-inflammatory effects in clinical trials (2). Another novel drug is gemfibrozil, which possibly exerts its antidepressant effects on humans through enhancing the BDNF pathway and activating CREB (1).

Bioactive components in food, fruits, and plants are constituents other than those necessary for life and meet basic nutritional needs and may be beneficial or deleterious for health status. Some are known as medicinal drugs due to their therapeutic and prophylactic effects, and some are still under trial (3). As psychiatric patients - including depressed ones - increasingly seek out complementary and alternative medications (1), and as the inflammatory mechanism in depression has recently become of interest (2), this text briefly addresses bioactive compounds in foods and plants that may be influential in depression through the inflammatory mechanism. Some supplements and herbs, like saffron and lavender, which have been reported in randomized controlled clinical trials to be effective, may exert their antidepressant effect through this system.

Naringin (Naringenin-7-neohesperidoside) is a flavonoid that is abundant in citrus fruits and has anti-inflammatory and antioxidant effects. Naringenin has been reported to improve depressive-like behaviors in mice by upregulating BDNF expression and restoring changes in the kynurenine pathway in the hippocampus and cortex (4). The effects of caffeine, a nutritional xanthine alkaloid that stimulates the central nervous system, on depression, particularly

* Corresponding author

Shahin Akhondzadeh, Pharm.D, PhD, FBPharmacoS

Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran

Tel: +98 21 5541 2222

Fax: +98 21 5541 9113

Email: s.akhond@neda.net

Received: Dec 20 2021

Accepted: Dec 21 2021

Citation to this article:

Shamabadi A, Akhondzadeh Sh. Bioactive Components for Depression: Naringin, Caffeine, Probiotics, Saffron and Lavender May Exert Antidepressant Effects Through Inflammation Modulation. *J Iran Med Council.* 2022;5(1):1-3.

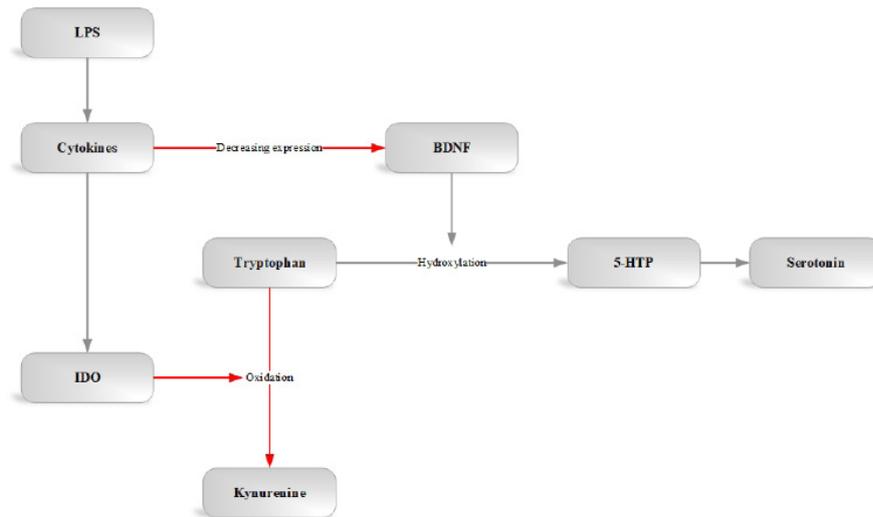


Figure 1. In the normal pathway, the enzyme tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan (5-HTP), the precursor of serotonin, with the help of brain-derived neurotrophic factor (BDNF). The injection of lipopolysaccharide (LPS), a bacterial endotoxin used to build an inflammation-related depression model, activates pro-inflammatory cytokines and then indoleamine 2,3-dioxygenase (IDO), which disrupt the normal pathway by reducing BDNF expression and tryptophan oxidation, respectively.

through the inflammatory mechanism, have been reported. Caffeine, like imipramine, improves lipopolysaccharide-induced inflammation in mice by regulating cytokines and increasing BDNF, thereby exerting its anti-depressive-like behavior effects (5). Another bioactive food component, probiotics, including bacteria and yeast, are living microorganisms found in fermented milk products and have recently been widely used orally. It has been shown to increase BDNF expression in male Wistar rats (6). The antidepressant effects of *Crocus sativus*, as an uncharacterized and non-homogenous natural product, have been reported in many clinical trials (7). Crocin is one of the principal secondary metabolites and constituents of saffron. Although most attention is paid to the glutamatergic system in the antidepressant effects of saffron, a pre-clinical study in rats found that crocin increased BDNF and CREB levels in the rat hippocampus (8). It also can prevent an induced decrease in BDNF levels in the hippocampus, like imipramine (9). Like saffron, many clinical studies have suggested antidepressant effects for *Lavandula angustifolia* as an uncharacterized and non-homogenous natural product with the most significant focus on the glutamatergic system (7). Its main active component is thought to be linalool. A pre-clinical study in mice reported that linalool could increase BDNF and TrkB levels in the hippocampus (10).

There is promising evidence of the effectiveness of bioactive food and herb compounds, and they may exert their antidepressant effect through this system. Unfortunately, standardization is not done in many herbal trials; however, only the effects of active ingredients were mentioned in this text. Another critical point is that bioactive compounds, like drugs, can cause interactions, which should be considered in the design of human trials. Taken together, agents acting on the inflammatory mechanism can be among the most promising alternative drugs with various therapeutic activities and mechanisms of action. Further high-quality studies in this area are recommended regarding the promising reported efficacy and the need for treatment in resistant patients who have a significant percentage (11-13).

Funding

This paper did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Keywords: Anti-Inflammatory agent, Dietary supplements, Herbalism, Inflammation, Pharmacotherapy

Conflict of Interest

The authors have no conflict of interest.

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