



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

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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

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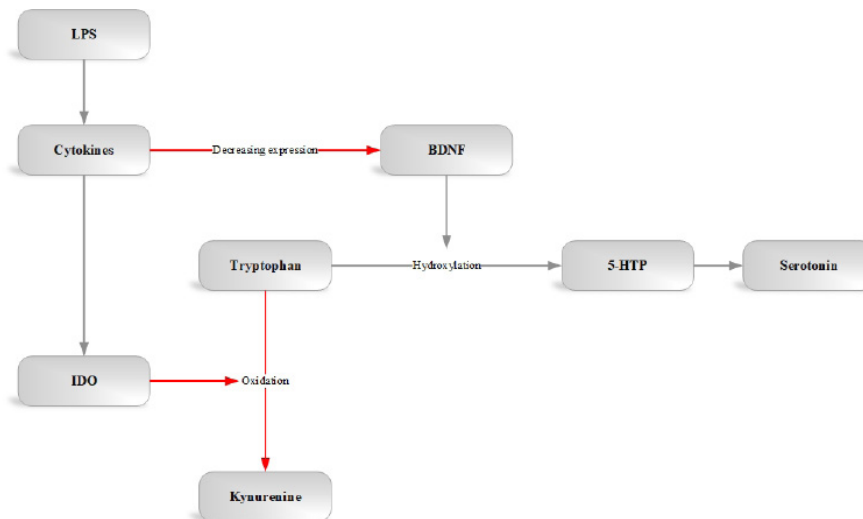


Figure 1. Conversion of Tryptophan to Serotonin.

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 Wister 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).

Figure 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.

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Conflict of Interest

The authors have no conflict of interest.

References

1. Shamabadi A, Akhondzadeh S. Advances in alternative and integrative medicine in the treatment of depression: A review of the evidence. *Arch Iran Med* 2021;24(5):409-18.
2. Kohler O, Krogh J, Mors O, Benros ME. Inflammation in depression and the potential for anti-inflammatory treatment. *Curr Neuropharmacol* 2016;14(7):732-42.
3. Teodoro AJ. Bioactive compounds of food: their role in the prevention and treatment of diseases. *Oxid Med Cell Longev* 2019;2019:3765986-.
4. Bansal Y, Singh R, Saroj P, Sodhi RK, Kuhad A. Naringenin protects against oxido-inflammatory aberrations and altered tryptophan metabolism in olfactory bulbectomized-mice model of depression. *Toxicol Appl Pharmacol*. 2018;355:257-68
5. Basu Mallik S, Mudgal J, Hall S, Kinra M, Grant GD, Nampoothiri M, et al. Remedial effects of caffeine against depressive-like behaviour in mice by modulation of neuroinflammation and BDNF. *Nutr Neurosci* 2021:1-9.
6. Mohammed SK, Magdy YM, El-Waseef DA, Nabih ES, Hamouda MA, El-Kharashi OA. Modulation of hippocampal TLR4/BDNF signal pathway using probiotics is a step closer towards treating cognitive impairment in NASH model. *Physiol Behav* 2020;214:112762.
7. Dome P, Tombor L, Lazary J, Gonda X, Rihmer Z. Natural health products, dietary minerals and over-the-counter medications as add-on therapies to antidepressants in the treatment of major depressive disorder: a review. *Brain Res Bull* 2019;146:51-78.
8. Vahdati Hassani F, Naseri V, Razavi BM, Mehri S, Abnous K, Hosseinzadeh H. Antidepressant effects of crocin and its effects on transcript and protein levels of CREB, BDNF, and VGF in rat hippocampus. *Daru* 2014;22(1):16.
9. Dorri SA, Hosseinzadeh H, Abnous K, Hasani FV, Robati RY, Razavi BM. Involvement of brain-derived neurotrophic factor (BDNF) on malathion induced depressive-like behavior in subacute exposure and protective effects of crocin. *Iran J Basic Med Sci* 2015;18(10):958-66.
10. Xu P, Wang K, Lu C, Dong L, Gao L, Yan M, et al. The protective effect of lavender essential oil and its main component linalool against the cognitive deficits induced by D-galactose and aluminum trichloride in mice. *Evid Based Complement Alternat Med* 2017;2017:7426538.
11. Jafari P, Ghanizadeh A, Akhondzadeh S, Mohammadi MR. Health-related quality of life of Iranian children with attention deficit/hyperactivity disorder. *Qual Life Res* 2011;20(1):31-6.
12. Nikoo M, Radnia H, Farokhnia M, Mohammadi MR, Akhondzadeh S. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Clin Neuropharmacol* 2015;38(1):11-7.
13. Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2016;41(2):214-9.