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Review Article

# Major Depressive Disorder and Brain: A Neurotrophic Factor in Terms of Epigenetics and the Application of Natural Substances

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## ABSTRACT

Major Depressive Disorder (MDD) is the main source of incapacity in developed nations (350 million individuals are influenced around the world), with wrecking side effects including depressed state of brain, loss of interest or happiness, official dysfunctions, psychomotor impediment, suicide ideation, and eating and sleep unsettling influences. Natural substances and cognitive enhancers are drugs, supplements, nutraceuticals and utilitarian nourishments that are implied to improve mental capacities, for example, insight, memory, knowledge, inspiration, consideration and focus for all BDNF is a big player. Thus their neglected importance and their application in MDD and BDNF should be revisited. This review discusses multiple aspects of MDD and BDNF in terms of epigenetics and natural substances as treatment options and will comprise of exploratory research with the purpose to propose a framework based on the literature review and the research findings to readers.

**Keywords:** Disorder; MicroRNA; Antidepressants; Drugs

## INTRODUCTION

The most disturbing factor in MDD is it may or may not present relapses and/or remissions. A number of foods and vitamins have been demonstrated to influence the epigenome including tomatoes, onions, garlic, broccoli, Brussels sprouts, apples, oranges, turmeric, cilantro, cinnamon, soybeans, coffee, green tea, black tea and vitamins A, B4, B6, B9, B12, C, and D. Foods and vitamins can shape epigenetic changes through a number of processes including: Influencing enzymes that catalyze DNA methylation and histone modifications, altering the availability of substrates for these enzymatic reactions affecting levels of miRNAs and modifying the composition of the gut microbiome, which transforms dietary compounds into molecules that influence epigenetic changes [1-4] The nutrition, including polyphenol, flavonoid compounds, and cruciferous vegetables possess multiple beneficial effects, and some can simultaneously change the DNA methylation, histone modifications and expression of microRNA (miRNA). This review mainly summarizes the information of epigenetic agents of DNMTs and HDACs inhibitors, miRNA mimics and antimiRs, as well as the natural nutrition. Some future perspectives related to the epigenetic epigenetic therapy with respect to natural endogenous substances are also included. Successful antidepressants incorporate SSRIs, SNRIs, a developing number of different kinds of present day antidepressants, (for example, bupropion and mirtazapine), TCA and MAOI antidepressants, ECT and an assortment of psychotherapies [5]. These are current treatment options.

## LITERATURE REVIEW

Drugs considered scholarly enhancers join dietary things and improvements, racetams, energizers, dopaminergics, cholinergics, GABA blockers, glutamate activators, serotonergics and hormones, etc. Supplements make neural connections and keep up the tangible framework by helping with handling unsaturated fats. Omega-3 effects both correspondence among cells and cell work [6-8]. Cell fortifications assistance to hold the mental limits longer, keep the psyche progressively energetic and shield it from oxidative damage. Amino acids help to convey the catecholamines and make preparation. Hormones increase neurogenesis and improve both memory encoding and audit. Iron makes hemoglobin, which transports oxygen to the cerebrum. Creatinine makes sure about ATP during transport.

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Lipoic destructive improves oxygen use and disease anticipation specialist reusing, improving memory and Germanium grows oxygen supply to the cerebrum. There is likewise moderate information mirroring the cooperations of characteristic substances and traditional medications [9-11]. Whether or not promising results have been found on *Crocus sativus*, *Eleutherococcus senticosus*, *Hypericum perforatum*, *Rhodiola rosea*, *Salvia miltiorrhiza*, *Vitis vinifera*, and *Withania somnifera* for their effect on BDNF modification, the amount of examinations of these botanicals is too low for drawing conclusive results. Botanicals considered for application in MDD are *Bacopa monnieri (L.) Pennell, Coffea arabica L, Crocus sativus L, Eleutherococcus senticosus Maxim, Camellia sinensis (L.) Kuntze* (green tea), *Ginkgo biloba L, Hypericum perforatum L, Olea europaea L.* (olive oil), *Panax ginseng, Rhodiola rosea L, Salvia miltiorrhiza Bunge, Vitis vinifera L, Withania somnifera (L.) Dunal*, and *Perilla frutescens etc (L.)* [12].

Melatonin (N-acetyl-5-methoxytryptamine) has been discovered as a hormone secreted by the pineal gland, even though it is also synthetized in various other organs, tissues, and cells. The circadian rhythm of melatonin is often used as an indicator phase position since it is a well-defined, high-amplitude rhythm controlled by the hypothalamic suprachiasmatic nuclei. Melatonin production is controlled by this endogenous circadian timing system. It peaks during the night and is suppressed by daylight. Mood spectrum disorders, including Bipolar Disorder (BD), Major Depressive Disorder (MDD), and Seasonal Affective Disorder (SAD), have been observed to be accompanied by circadian dysregulation as well as dysregulation in melatonin secretion. Melatonin definitely promotes BDNF expression and that is shown in several studies [2]. Melatonin and resveratrol ameliorates the BDNF expression of hippocampal protein [13].

Palmitoylethanolamide (PEA) is a lipid mediator used in the clinic for its neuroprotective, anti-neuroinflammatory and analgesic properties [14]. Pretreatment with PEA signicantly reduces iNOS, glial brillary acidic protein expression and apoptosis, and restores neuronal NO synthase as well as BDNF. PEA stimulates the expression of neurotrophic factor BDNF [15].

PEA increases the expression of BDNF BDNF, a representative neurotrophic factor in the central nervous system, in the hippocampal dentate gyrus, and most BDNF-positive cells were also stained with anti-glial fibrillary acidic protein (one of the major intermediate filament proteins of mature astrocytes). Identifying biological targets in major depressive disorder MDD is a critical step for development of effective mechanism-based medications. The epigenetic agent Acetyl-L-Carnitine (ALC) has rapid and enduring antidepressant-like effects in LAC-deficient rodents. LAC levels were decreased in patients with MDD *versus* age- and sex-matched healthy controls in two independent study centers. The degree of LAC deficiency reflected both the severity and age of onset of MDD. The lowest LAC levels were found in patients with treatment-resistant depression, whereby history of emotional neglect and being female predicted decreased LAC levels. The LAC may serve as a candidate biomarker to help the diagnosis of a clinical endophenotype of MDD that supplementation of LAC exerts rapid antidepressant actions, at least in part, by acetylating histones to regulate the expression of key genes important for synaptic plasticity, increasing the proneurogenic molecule BDNF to high levels and a critical regulator of synaptic glutamate release, the metabotropic glutamate receptor of class-2, mGlu2.

## DISCUSSION

Zinc deficiency has been implicated in the endocrine pathway of depression. A zinc-deficient diet induced high levels of serum cortisol concentration in rats. Persistently high levels of cortisol have been implicated in the development of depression *via* hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Increased plasma cortisol levels could, therefore, potentially mediate the relationship between zinc deficiency and depression. Lastly, the potential antidepressant properties of zinc may be related to its function as an antagonist of the receptor and involvement in the l-arginine-Nitric Oxide (NO) pathway as an inhibitor. NMDA has been therapeutically targeted in clinical and preclinical studies of depression treatment, as growing evidence supports the presence of disrupted glutamate homeostasis and neurotransmission in depressed subjects [16-20].

The coffee plant, a woody enduring tree developing at higher elevations, has a place with the group of Rubiaceae. In spite of the fact that beans are especially wealthy in caffeine, different constituents are available in a significant sum, including tocopherols and caffeine corrosive subsidiaries, for example, chlorogenic corrosive [12]. Three examinations researched the *in vitro* impact of caffeine on BDNF. Specifically, caffeine upregulated the BDNF protein levels in mouse hippocampal cuts (100 μM for 5 minutes) , expanded the BDNF discharge in hippocampal neurons, and proficiently viabled the BDNF isoform I and IV articulation within the sight of KCl (10 mM) in cortical neurons Caffeine adjusts CREB-subordinate quality articulation in creating cortical neurons [21].

*Withania somnifera (L.)* Dunal, similarly called *Ashwagandha* or *Indian ginseng* (Solanaceae), is a standard Ayurvedic fix reputed to be useful as an antistress and memory enhancer. Pretreatment with a boozer concentrate of *Ashwagandha* leaves (100 mg, 200 mg, and 300 mg/kg for 7 days) in a general sense prevented the effects in light of the scopolamine treatment (3 mg/kg, for instance, the lessening of the mRNA enunciation of BDNF transcript variety 1 and of pro BDNF and mBDNF protein explanation at all the centers attempted. As a matter of fact, posttreatment at 200 mg/kg was unfit. Protective occupation of *Ashwagandha* leaf focus and its part withanone on scopolamine-impelled changes in the cerebrum and psyche gathered cells. Withanolide-propelled concentrate from the *Withania somnifera* root (methanol-water 25:75, v/v) was evaluated on provoked hypobaric hypoxia in rodents. Animals dealt with when hypobaric hypoxia with 200 mg/kg of the concentrate showed an extended enunciation of BDNF and a gigantic decrease in lethargy and route length in the MWM test.

*Rhodiola rosea L.* (Crassulaceae) has a long history of usage as a helpful plant in a couple of traditional medications. Inside and out around 140 blends were isolated from roots and rhizome - monoterpene alcohols and their glycosides, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonlignans, proanthocyanidins and gallic destructive subordinates. Studies on limited organs, tissues, cells and mixes have revealed that *Rhodiola* courses of action show adaptogenic sway including, neuroprotective, energizer, anxiolytic, nootropic, effects and CNS empowering activity. Salidroside (SA, syn. rhodioloside). One *in vitro* assessment surveyed the effect of SA on BDNF displaying that the unadulterated compound incited mesenchymal undifferentiated cells to isolate into dopaminergic neurons. SA treatment (100 μg/mL) for 1-6 days on a very basic level extended the BDNF mRNA levels while at 12 days, an opposite effect was found. In an unforeseen manner, the effect on the BDNF protein levels was even more sturdy since it was so far present after 12 days. *In vivo*, the treatment for 5 days (12 and 24 mg/kg) with SA or fluoxetine hindered the improvement of the downturn like direct and of the downregulation of BDNF protein levels in the hippocampus impelled by a lone imbuement of LPS [22-28]. Taking everything into account, *Rhodiola rosea* has traditional and pharmacological verification of usage in depletion, and rising confirmation supporting acumen and mentality [29].

*Ginseng* radix contains the whole or cut dried establishment of *Panax ginseng* and contains at any rate 0.4% of the total of ginsenosides (Rg1) and (Rb1). Ginsenosides are triterpenoid saponins which are the rule at risk for the natural activities of ginseng removes. *Panax ginseng* expel or unadulterated blends applied an advantageous result in like manner on the scopolamine animal model. As a general rule, Wild Ginseng (WG) roots (200 mg/kg, i.p.) normalized the mRNA level of BDNF in the rat hippocampus of the scopolamine-treated assembling, similarly as reducing the flight idleness in the MWM test. In like way, pretreatment with ginsenosides (Rg5) and (Rh3) (5,10 and 20 mg/kg, per os) subdued the decline of mBDNF protein enunciation started by scopolamine implantation (1 mg/kg, i.p.) and lessened the torpidity time in MWM.

The potential neuroprotective effect of specific constituents of green tea leaves, including catechins, was investigated in two *in vitro* assessments. L-Theanine pretreatment (500 μM) applied a guarded effect by on a very basic level choking the downregulation of BDNF protein due to the treatment with two contamination related neurotoxicants (rotenone and dieldrin) in the human cell line SH-SY5Y. Moreover, pretreatment with GT catechins, for instance, Epicatechin (EC) and (+) catechin, thwarted the decline of mBDNF and the extension in the predecessor structure provoked by the risky HIV (Human Immunodeficiency Disease) protein Tat [30-35].

*Ginkgo biloba* is an old Chinese tree having a spot with the social event of Ginkgoaceae, made for its thriving moving properties. In spite of the fact that the two leaves and seeds are beginning at now utilized as home created tranquilize in China, in different nations, leaves are viewed as the exceptional wellspring of dynamic checks and dried green leaves are utilized for giving pharmaceutical definitions or centers as segments of sustenance supplements. *Ginkgo biloba* and its constituents were reviewed on BDNF in three *in vitro*, eight *in vivo*, and one clinical assessments. Ginkgo biloba leaf evacuate (EGb761, 100 μg/mL) reestablished the degrees of BDNF protein (both genius and make structure) in cells excited with real medium arranged to actuate amyloid β-peptide Aβ clarification. Relationship of individual EGb761 constituents, explicitly, Ginkgolides A (GA), B (GB), C (GC), and J (GJ) and 10 μg/mL bilobalide, expanded the degrees of BDNF by following a relative model. As needs be, flavonol-advanced concentrate containing quercetin, kaempferol, and isorhamnetin (50 μg/mL) fundamentally reestablished BDNF protein articulation in twofold transgenic APP/PS1 essential neurons. Also, 100 μg/mL of YY162, a licensed equation comprising of terpenoid-fortified *Ginkgo biloba* and ginsenoside Rg3, forestalled the decrease of BDNF levels incited by 48 h of Aroclor 1254 in SH-SY5Y neuroblastoma cell line [36].

*Crocus sativus L.* has a place with the Iridaceae family; generally known as saffron and are broadly developed in Iran and utilized in current and conventional drugs. The shade of saffron is generally because of the carotenoid named crocin, which is considered among the dynamic standards for the most part answerable for neuroprotective action.

Two *in vivo* examinations researched the impact of *Crocus sativus* on BDNF articulation. Crocin organization (12.5 mg/kg, i.p.) for 21 days to credulous male Wistar rodents applied an energizer impact and essentially expanded the interpretation levels of BDNF in the hippocampus [37]. Similarly, constant treatment with *C. sativus* watery concentrate (40,80 or 160 mg/kg/day, i.p.), upgraded the quality and protein levels of BDNF in the rodent hippocampus. In addition, at 40 and 160 mg/kg/day, a stimulant movement was likewise watched [38].

Magnesium has a strong association with BDNF explicitly the threonate structure. One examination found attempted measurements of magnesium (10,15 and 20 mg/kg) diminished hyperactivity in the open field test in rodents in the Olfactory Bulbectomy (OB) model of distress. Since the extended hyperactivity in the open field test is seen as a result of worry just as anxiety, these results appear to reinforce the general hypothesis that supports both the high and anxiolytic activities of magnesium [39,40]. The examinations indicated that relentless association of magnesium was connected with a development in the BDNF and GluN2B subunit levels in the hippocampus, which shows changes that partner with improved neuroplasticity [41]. Along these lines, extended BDNF and GluN2B subunit levels in the amygdala may show the revamping of synaptic affiliations hurt by bulbectomy and the normalization of neural transmission between the amygdala and other cerebrum structures [42]. Magnesium could potentially exert antidepressant effects through its role in serotonergic, noradrenergic and dopaminergic neurotransmission, increased expression of BDNF and modulation of the sleep–wake cycle through augmentation of the biosynthesis of melatonin. Magnesium l-threonate was specifically created to cross the brain's protective filter, the blood-brain barrier. Another brain-enhancing property of magnesium l-threonate is that it increases brain plasticity. A key finding from the current study was that elevation of brain magnesium enhanced the retention of extinction of fear memories

without enhancing, impairing, or erasing original fear memory. This correlated with selective enhancement of NMDAR signaling, BDNF expression, and synaptic plasticity in the PFC, but not in the basolateral amygdala. This unique region-specific pattern of action might stem from a lack of sensitivity of NMDAR and its signaling, within the amygdala, to an elevation in the extracellular magnesium concentration in the brain [2]. Effects of elevation of brain magnesium on fear conditioning, fear extinction, and synaptic plasticity in the infralimbic prefrontal cortex and lateral amygdala. Zinc monotherapy in moderate dosage seems improving mood through increasing BDNF levels [43].

*Bacopa monnieri (L.)* Pennell is an individual from Scrophulariaceae customarily utilized in Ayurvedic medication for epilepsy and asthma. The best-portrayed mixes happening in the entire plant are dammarane-type triterpenoid saponins known as bacosides (generally bacoside A), which are viewed as the principle liable for the organic action. Two examinations researched the defensive impact of *Bacopa Monnieri* Separate *in vitro*. In PC12 cells, pretreatment with a hydroalcoholic separate totally forestalled the decrease of BDNF mRNA levels related with cell harm prompted by scopolamine or sodium nitroprusside. *Bacopa Monnieri* (BM)is a therapeutic Ayurvedic herb [44].

The high number of articles distributed (more than one hundred compositions for 14 botanicals) bolsters the developing enthusiasm for the utilization of regular items as BDNF modulators. The examinations detailed fortify the theory that botanicals might be viewed as valuable modulators of BDNF in CNS illnesses, without high reactions. Further clinical examinations are obligatory to affirm botanicals as preventive specialists or as helpful adjuvant to the pharmacological treatment. Initially, considering the multifaceted nature of the BDNF framework progressively refined examination of the various components both at interpretation and translational levels is obligatory. In fact, not many investigations report the BDNF isoform or the structure estimated, and, at times, the molecules load of the band inspected doesn't relate to either the develop or the antecedent structure. Furthermore the quantity of clinical investigations is restricted since hardly any clinical preliminaries have been found in writing. Among them, the first was done in quite a while following treatment with *Ginkgo biloba L.* extract and the second was acted in depressed patients treated with *Hypericum perforatum L.*, though the others were acted in solid subjects [45,46].

Several studies have shown that vitamin D is essential for normal brain development and function, and vitamin D deficiency has been linked with neurological disorders, including depression. Vitamin D is also involved in the initial biosynthetic stages of serotonin, a neurotransmitter which has been implicated in both depression and the mechanism of action of antidepressant drugs. A study found decreased hippocampal levels of BDNF in a preclinical model of depression, and these were normalized by vitamin D administration. On the other hand, multiple steps in require magnesium as a cofactor, including vitamin D binding to vitamin D binding protein, 25(OH)D synthesis, 1,25(OH)2D synthesis, 25-hydroxylase synthesis, and vitamin D receptor expression. In addition, serum 1,25 (OH)2D levels remain low in individuals with magnesium deficiency even following vitamin D intake. Magnesium deficiency has also been found to reduce parathyroid hormone production and the number of vitamin D receptors in target cells [1].

The influence of the gut microbiota on has been convincingly demonstrated in rodents. In the absence of gut bacteria, the central expression of brain derived neurotropic factor, BDNF, and N-Methyl-D-Aspartate Receptor (NMDAR) subunits are reduced, whereas, oral probiotics increase brain BDNF, and impart significant anxiolytic effects. The prebiotic-mediated proliferation of gut microbiota in rats, like probiotics, increases brain BDNF expression, possibly through the involvement of gut hormones. The effect of GOS on components of central NMDAR signaling was greater than FOS, and may reflect the proliferative potency of GOS on microbiota. It looks like that prebiotics probiotics and Fructo-Oligosaccharides (FOS), Galacto-Oligosaccharides (GOS) provide a sound basis to further investigate the utility of prebiotics in the maintenance of brain health and adjunctive treatment of neuropsychiatric disorders [47]. Augmentation of SSRI treatment with probiotic bacteria *Lactobacillus Plantarum* 299 v improves cognitive performance and decreased KYN concentration in MDD patients.

Omega-3 unsaturated fats (i.e., Docosahexaenoic Acid; DHA) direct sign transduction and gene expression, and shield neurons from death. In this investigation we inspected the limit of dietary omega-3 unsaturated fats supplementation to assist the brain with coping with the impacts of awful injury. It is realized that BDNF encourages synaptic transmission and learning capacity by tweaking synapsin I and CREB. Supplementation of omega-3 unsaturated fats in the eating regimen neutralized the entirety of the examined impacts of FPI, that is, standardized degrees of BDNF and related synapsin I and CREB, decreased oxidative harm, and balanced learning handicap [4].

Curcumin, as a new member of the histone deacetylase inhibitors, can inhibit the expression of class I HDACs (HDAC1, HDAC3, and HDAC8), and can increase the expression of Ac-histone H4 in Raji cells. Curcumin plays an important role in regulating B-NHL cell line Raji cell proliferation and apoptosis. Curcumin is the principal curcuminoid found in turmeric (*Curcuma longa*), a spice frequently used in Asian countries. Given its anti-inflammatory and antioxidant properties, it has been hypothesized that curcumin might be effective in treating symptoms of a variety of neuropsychiatric disorders, such as depression. A number of meta-analyzes indicated the effectiveness of the combined use of curcumin with antidepressants in the treatment of depression. The mechanism of action of curcumin, as well as the prospects for its further use are considered [48].

The antidepressant active ingredients of Traditional Chinese Medicine (TCM), identified can be generally divided into saponins, flavonoids, alkaloids, polysaccharides and others. Albiflorin, Baicalein, Berberine chloride, beta-Asarone, cannabidiol, Curcumin, Daidzein, Echinocystic Acid (EA), Emodin,

Ferulic acid, Gastrodin, Genistein, Ginsenoside Rb1, Ginsenoside Rg1, Ginsenoside Rg3, Hederagenin, Hesperidin, Honokiol, Hyperoside, Icariin, Isoliquiritin, Kaempferol, Liquiritin, L-theanine, Magnolol, Paeoniflorin, Piperine, Proanthocyanidin, Puerarin, Quercetin, Resveratrol (trans), Rosmarinic acid, Saikosaponin A, Senegenin, Tetrahydroxystilbene glucoside and Vanillic acid are promising candidates to discover a drug to treat MDD and other neurologic and psychiatric diseases and disorders. One of the best example of TCM with respect to increasing BDNF levels is Yue; an ethanol extract of Yueju pill, a Traditional Chinese Medicine herbal formula widely used to treat mood disorders, demonstrates rapid antidepressant effects similar to ketamine, likely *via* instant enhancement of Brain-Derived Neurotrophic Factor (BDNF) expression in the hippocampus. One of five individual constituent herbs of Yueju, Gardenia Jasminoides Ellis (GJE) shows a significant effect. The antidepressant response starts at 2 hours after GJ administration. Similar to Yueju and ketamine, a single administration of GJ significantly reduces the number of escape failures in the learned helplessness test. Furthermore, GJ decreases latency of food consumption in the novelty suppressed-feeding test. GJ has rapid antidepressant effects, which are associated with the elevated expression of BDNF in the hippocampus [49-52].

## CONCLUSION

There is a growing interest and extensive work with respect to cannabinoid use in psychiatric patients suffering from MDD and cannabis-BDNF interactions. The grown-up mammalian brain can create new neurons in a procedure called grown-up neurogenesis, which happens chiefly in the Subventricular Zone (SVZ) and in the Hippocampal Dentate Gyrus (HDG). BDNF flagging and Cannabinoid type 1 and 2 Receptors (CB1R and CB2R) have been appeared to autonomously regulate neurogenesis, yet how they may associate is obscure. A growing body of significant research suggests CBD oil can function as a strong component of a natural plan to alleviate anxiety. Strong preclinical evidence suggests positive mental health benefits of CBD oil that include decreased feelings of social isolation, improved autistic tendencies, and a lessening of Posttraumatic Stress Disorder (PTSD) symptoms.

Antidepressants frequently come up short since patients show late relapses and short-reductions and with adverse and side effects breaking up all metabolisms. Since there is no concoction medicate to build the degree of BDNF one should seriously think about to embed a few botanicals, unsaturated fats, minerals, substance components, probiotics, prebiotics, flavonoids into treatment instruments as for MDD due to their apheliotropic effect to increase the levels of BDNF.

In spite of the fact that standardization of the botanicals and natural endogenous and exogenous substances is as yet problematic the characteristic supply offers some effective planned and even some endogenous items might be utilized for forestalling CNS distortion or as a helpful adjuvant to the pharmacological treatment regarding so far unsolved issue called Major Depressive Disorder.

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