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A review article

Promising Therapeutic Targets for Major Depressive disorder: A Narrative Review

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ABSTRACT

Background: Major depressive disorder (MDD) is one of the most common psychiatric diseases, affecting millions of people worldwide. Evidence confirms that depression is a multifactorial disease. Consequently, the traditionally prescribed antidepressants such as selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors and tricyclic antidepressants, which only depend on modulating the level of monoamines, face many obstacles. These drugs are of moderate efficacy and have a delayed onset of action (4-6 weeks) in addition to an increased rate of resistance against them. These obstacles make it critical to explore novel pathways and therapeutic targets for the treatment of the disease. The literature is flooded with massive numbers of studies investigating many targets with potential antidepressant effects. This review summarizes recent clinical and preclinical studies discussing the most promising therapeutic targets for treatment of MDD, including proinflammatory cytokines, brain-derived neurotrophic factor, gut microbiota, the psychedelic agent (psilocybin) and 5HT-2A receptor.

Conclusions: This review summarizes a large number of recent studies investigating some of the most promising therapeutic targets for MDD and aims to highlight the inconsistent results that impede the approval of these agents for treatment of the disease.

Key words: cytokines; brain-derived neurotrophic factor; dysbiosis; psilocybin; 5HT2A

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric illness affecting approximately 280 million people in the world. Low mood and anhedonia (loss of interest or pleasure in usual daily activities) are core features of this disease besides concentration, sleep and appetite problems and recurrent thoughts of suicide or attempts to commit it [١].

Treatment of MDD relies on approved antidepressants such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors**.** However, these antidepressants display moderate efficacy with only a 35% full remission rate after using the first antidepressant [٢]**.** In addition, more than one-third of depressed patients are considered to have treatment-resistant depression which describes patients with MDD who do not adequately respond to at least one antidepressant for at least six weeks [٣]**.** Furthermore, the currently prescribed antidepressants have a delayed onset of action (about 4-6 weeks) and their chronic use may result in sleep disturbances, sexual dysfunction, emotional blunting, and cognitive impairment which may impede patients' quality of life and therapy adherence [4].

Previous drawbacks suggest that mechanisms other than monoamine deficits are implicated in the pathophysiology of depression and that targeting these mechanisms may provide more effective candidates for the treatment of depression. As a result, the literature is flooded with studies investigating different pathways and potential therapeutic targets for the treatment of depression, such as proinflammatory cytokines, brain-derived neurotrophic factor (BDNF), the gut microbiota and the psychedelic agent psilocybin. This review summarizes the role of these systems in the pathogenesis of depression and the recent progress concerning their role as potential therapeutic targets for MDD. We searched PubMed, Scopus and Google Scholar to collect the relevant data and tried to cite the most recent studies as much as possible.

Proinflammatory cytokines:

Over decades, evidence has mounted confirming that depression is associated with dysregulation of the immune system. One of the immune system's most extensively researched elements in depression is cytokines. A large meta-analysis revealed that pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), are elevated in patients with MDD [5].

Central cytokines are produced by microglia (the specialized brain immune cells) and other brain cells where they are involved in many functions, including neurogenesis and synaptic transmission**.** In addition, peripheral cytokines can cross the blood-brain barrier (BBB) through the fenestrated capillaries of circumventricular organs and choroid plexus devoid of tight intercellular junctions or through the BBB when its permeability is disturbed by some diseases. Cytokines may also bind to receptors localized on peripheral afferents of the vagus nerve. Furthermore, they may stimulate the endothelial lining of cerebral blood vessels or perivascular macrophages which then release proinflammatory cytokines into the brain parenchyma [6]**.**

Cytokines may activate the indoleamine 2,3-dioxygenase (IDO) enzyme which catabolizes tryptophan (the precursor of serotonin) into kynurenine resulting in serotonin depletion as well as elevating oxidative stress in the brain. In addition, cytokines can also modulate glutamate level resulting in glutamic neurotoxic effects as well as disturbing the hypothalamo-pituitary-adrenal (HPA) axis. Disturbance of HPA in the form of altered cortisol circadian rhythm, hyperactivity of HPA axis, and dysfunctioning of the feedback response is bidirectionally associated with stress which is an established risk factor for the development of depression [7].

Consequently, it is plausible that the anti-cytokines agents have been supposed to express antidepressant effects. Anti-TNF-α therapy significantly improved symptoms of anxiety and depression accompanied by inflammatory bowel diseases (IBD) on the hospital anxiety and depression scale in a 5 year-observational study [8]. In a meta-analysis of nine randomized clinical trials (RCTs) conducted on patients with inflammatory diseases associated with depressive symptoms, anti-cytokines drugs displayed a modest but significant improvement of depressive symptoms especially in patients with severe depressive symptoms at baseline. This effect is comparable to the antidepressant efficacy produced by SSRI in patients with MDD as estimated by other meta-analyses. Ustekinumab (an anti-IL-12/23 antibody) and siltuximab (an anti-IL-6 antibody) displayed the most statistically significant antidepressant effect in this mega-analysis [9]. Further studies are needed to establish whether the improvement in depression following the use of anti-cytokine drugs is due to modulation of depression pathways or if it is a result of the improvement of the comorbid autoimmune disease.

On the other hand, cytokines such as TNF-α and IL-6 may exhibit some neuroprotective functions [10]. This notion may explain the unexpected findings reported by some studies following the blocking of these cytokines. Thillard et al. [11] reported that patients treated with infliximab (anti TNF-α antibody) for rheumatoid arthritis, IBD, and other inflammatory disorders were at higher risk of developing psychiatric disorders 3-9 times more than those who were not exposed to infliximab. In this cohort study, MDD was the most common psychiatric adverse event affecting approximately 10% of infliximab-treated patients in addition to a higher risk of suicidal attempts especially in RA patients. Similarly, tocilizumab (IL-6 inhibitor) was associated with worse depressive symptoms following its use in patients who underwent hematopoietic stem cell transplantation compared to the control group [12]. However, a systematic review of 16 studies estimated that the incidence of depression and anxiety in IBD patients treated with anti-cytokine agents is < 1%. Jain et al. [13] concluded that the evidence was insufficient to establish the association between anti-cytokine

agents and the incidence of adverse psychiatric events.

Brain-derived neurotrophic factor (BDNF):

BDNF is a growth factor that plays a crucial role in neurogenesis, development, and maintenance of synaptic plasticity which has gained much interest as an essential contributor in initiating depression. BDNF enhances dendritic growth and branching and is involved in neuronal regeneration and differentiation. In addition, it displays antiapoptotic activity and protects neurons against glutamate toxicity. Both peripheral tissues and central structures (primarily the limbic system, hippocampus, and hypothalamus) release BDNF which mediates its actions through binding to tropomyosin receptor kinase B (TrkB) receptor. This interaction triggers dimerization and autophosphorylation of the receptor intracellular tyrosine residues at several sites, followed by evoking the downstream signaling of different pathways including: **(1)** phospholipase C-γ (PLC_{γ})–Ca^{2+}, **(2)** mitogen-activated protein kinase (MAPK)/ extracellular signal-regulated kinase (ERK)/ cAMP response element binding protein (CREB)**, (3)** phosphatidylinositol 3-kinase (PI3K)-Akt pathways [14]**.**

A diminished level of BDNF in the brain and blood was detected in patients diagnosed with MDD while the blood level of BDNF increased upon treatment with antidepressants [15]. Studying the brain postmortem samples of depressed patients who committed suicide also revealed a significant reduction in the expression of protein and mRNA of BDNF and TrkB in the hippocampi of those patients [16]. The role of BDNF/ TrkB signaling is more prominent in promoting the action of antidepressants. Recently, Casarotto and colleagues [17] have demonstrated that different antidepressants (such as fluoxetine, imipramine, and esketamine) bind directly to the TrkB receptor. Antidepressant-receptor interaction elicits conformational changes in the receptor followed by increasing the translocation of TrkB to the cell surface facilitating BDNF signaling.

Unfortunately, therapeutic benefit of BDNF is limited by its short elimination half-life ($t_{1/2}$) (< 10 minutes) and inability to penetrate the BBB owing to its large size (27 kDa). The natural flavonoid 7,8-dihydroxyflavone (small molecules that stimulate the TrkB receptor) can mimic the functions of BDNF. These molecules have a longer $t_{1/2}$ (≈134 minutes), a smaller size (254 Da), and have shown promising results in the treatment of various central and peripheral diseases [18]. However, studies show inconsistent results regarding the mechanism of action and efficacy of 7,8-dihydroxyflavone as antidepressants. Liu and colleagues [19] reported that 7,8-dihydroxyflavone could bind to the TrkB receptor evoking dimerization and autophosphorylation of the receptor, while this compound failed to activate this receptor in another cell culture study [20].

In animal models of depression, 7, 8-dihydroxyflavone expressed an antidepressant effect in mice as demonstrated by the shortening of the immobility time in the tail suspension test and forced swim test (FST) [21]. Additionally, a combination of fluoxetine and 7,8-dihydroxyflavone had a synergistic effect on the alleviation of depressive symptoms in perimenopausal mice. This combination activated the PI3K/Akt/phosphorylated mammalian target of rapamycin (mTOR) pathway and increased the expression of BDNF and TrkB in the cortex and the hippocampus [22]**.** In contrast to the results of the previous models, a large dose of 7,8-dihydroxyflavone did not affect either the expression of genes encoding for serotonin receptors or the expression of BDNF and TrkB. In addition, this molecule decreased serotonin levels in the cortex and hippocampus of mice and had no effect on the immobility time in the FST. The only beneficial effect induced by 7,8-dihydroxyflavone in this model was the significant reduction in the expression of the proapoptotic gene (Bax) [23].

Gut dysbiosis:

Gut dysbiosis is defined as an imbalance in the composition of gut microbiota (bacteria, archaea, viruses, and fungi) due to the deficiency of beneficial microbiota or the overwhelming of harmful ones leading to disturbance in the overall diversity and functions of these microorganisms. Gut dysbiosis is suggested to contribute to the pathogenesis of depression, even though the definite cause-and-effect relationship is not clear till now [24]. Evidence supporting this association has stemmed from observational studies which reported that antibiotic exposure increased the risk of psychiatric disorders [25]**.** Another piece of evidence supporting this association is the relationship between depression and IBD. Depression is prevalent in at least 20% of patients suffering from IBD, where gut dysbiosis is involved in the damage of the intestinal barrier and the induction of abnormal immunological reactions [26]. The association between gut microbiota and brain disorders established what is called the

microbiota-gut-brain axis, describing the bidirectional communication between the gut and the brain. The gut microbiota produces neuroactive compounds and active metabolites such as short-chain fatty acids which could modulate neuroplasticity and immune responses in animal models. These compounds, besides microorganisms' cell components, could damage and disrupt the integrity of the intestinal epithelial barrier leading to the leak of microbiota- related active molecules into the lamina propria, where they disturb the enteric nervous system (ENS). Disturbance of ENS activity leads to disturbance of signaling across the extrinsic neurons connecting the gut to the brain. Furthermore, microbiota-related active molecules could reach the brain through the afferents of the vagus nerve which is suggested to be the most direct pathway for microbiota signals to access the brain [27].

Modulation of the gut microbiota has been targeted as a potential therapeutic approach for depression. RCTs have revealed the efficacy of probiotics, which are beneficial live bacteria, in the treatment of MDD [28]. Most probiotics contain *Lactobacilli Bifidobacteria* species, the anti-inflammatory commensal bacteria, but the authors of a comprehensive review identified 178 species and subspecies of bacteria to be effective in the treatment of depression in humans and animal models [29]**.** Although some RCTs showed that probiotics were not superior to placebo in the treatment of depression, it is important to note that the efficacy of probiotics is affected by cofounders such as age, geographical area, depression phenotype, and comorbidities. In addition, the interaction between different bacterial species leads to synergism which enhances the antidepressant effect of probiotics. Consequently, the administration of multi-species probiotics will give better results than the use of single species [24].

Prebiotics such as fructo-oligosaccharides and galactooligosaccharides are substrates that are utilized by beneficial gut bacteria allowing their growth. Chronic administration of prebiotics could alleviate depressive-like behaviour in mice [30]. However, they did not show efficacy in RCTs [28]. Prebiotics are not directly beneficial to the body. Instead, they allow the growth of beneficial bacteria which can promote host health. Consequently, it is recommended to use a probiotic and prebiotic combination which is called symbiotic **[**24].

Psilocybin and 5-HT2A receptors:

Psilocybin is a psychedelic agent extracted from mushrooms and has been used over centuries for spiritual and medical purposes. Recent studies suggest that psilocybin is promising for the treatment of some neuropsychiatric diseases. It has been found to express a rapid and sustained antidepressant effect in patients with treatment-resistant depression and life-threatening cancer [31]. Similar results were revealed by many RCTs in MDD patients. A single moderate dose of psilocybin associated with psychotherapy could alleviate MDD symptoms within two days post-treatment, an effect which lasted over 14 days [32]**.** Furthermore, the antidepressant effect of two doses of psilocybin was even preserved over 12 months, with a 58% remission rate at the end of the study. Additionally, the authors reported a significant improvement in the suicidal ideation score one week after administration of the first dose, although the change in this score did not remain significant till the end of the 12th month [33]**.** The persistent antidepressant effect of psilocybin is superior to that of ketamine, another rapidly acting antidepressant approved for treatment-resistant depression, as its antidepressant effect seemed to drop one week after administration of a single dose [34]. The results of animal studies are consistent with the results of the RCTs. A single dose of psilocybin alleviated anhedonia and upregulated synaptic plasticity markers in the hippocampus and prefrontal cortex of the animals 24 to 48 hours following dose administration and these changes were preserved for seven days [35, 36]**.** The mechanisms underlying the antidepressant effect of psilocybin have not been fully understood until now. Rats treated with low doses of psilocybin displayed behaviors associated with 5-HT2A receptor activation, such as wet dog shaking and back muscle contraction with an overall modest antidepressant effect. These rats did not show any behaviors associated with activation of 5-HT1A or 5-HT2C receptors [37]. Psilocybin markedly elevated the extracellular level of serotonin in the frontal cortex of rats. Ten mg/kg of psilocybin significantly increased the level of glutamate and GABA neurotransmitters. Activation of 5-HT2A receptors may explain these results, as the release of glutamate from the thalamocortical neurons and the release of GABA from the cortical interneurons are mediated through 5-HT2A receptors. In addition, glutamate, released under activation of 5-HT2A receptors, acts on pyramidal AMPA receptors which enhances the release of serotonin in the frontal cortex. However, the authors

of this experiment reported that activation of the 5-HT1A receptors could not be excluded, as both 5-HT1A and 5-HT2A receptors are 80% co-expressed on the same cortical neurons in rats and could modulate the release of neurotransmitters from different neurons [38]. Furthermore, psilocybin rapidly upregulated synaptic plasticity-related genes in the prefrontal cortex and hippocampus of rats with greater effect on genes of the prefrontal cortex where 5-HT2A are more expressed [39]. On the other hand, Hesselgrave et al. [35] reported that ketanserin (an antagonist 5-HT2A and 5-HT2C receptors) could not prevent the antidepressant effect produced by psilocybin in stressed mice.

The risk of dependence, abuse, and disturbance in perception, cognition, and mood previously linked with the use of psychedelic drugs represents a stigma against the wide use of psilocybin. Classic psychedelics were included in Schedule I when the Controlled Substances Act (CSA) was established in 1970, but their potential abuse has not been thoroughly investigated by novel methodologies. Contrarily, a large body of evidence confirms that psychedelic agents, especially psilocybin carry a minimal risk of dependence, compulsive use, and substance abuse. Interestingly, psychedelic drugs displayed a promising anti-addictive role in the treatment of alcohol and tobacco use disorders [40]. As regards physical adverse effects, clinical trials that investigated the safety of psilocybin reported transient elevation of systolic blood pressure, while mild to moderate headache was the most prevalent adverse effect [32, 33]**.** Overall, these trials, unfortunately, included a small number of patients and more studies with larger sample sizes are needed to establish the safety of psilocybin.

CONCLUSIONS

MDD is a multifactorial disease with many biological pathways contributing to its pathogenesis that intertwine with each other. A large body of evidence displayed the promising antidepressant effect of the drugs targeting the proinflammatory cytokines, BDNF, gut microbiota, and 5HT2A receptor. Most studies supporting this conclusion are observational studies, preclinical studies, and cell culture studies. Unfortunately, most RCTs in this context are non-comparative, include a small number of participants, or include participants with other comorbid diseases. Based on the previous studies, anti-cytokine drugs, the natural 7,8-dihydroxyflavone, probiotics, and prebiotics seem to be good adjuncts that synergize the efficacy of traditional antidepressants. Psilocybin is a highly promising antidepressant. It expresses a more sustainable antidepressant effect with lower adverse effects than ketamine which is approved for treatment-resistant depression. Overall, wide scale randomized double-blind controlled clinical trials comparing the efficacy and safety of these drugs to traditional antidepressants are critically needed to hasten the development of new therapeutics for MDD.

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Author Contributions:

All authors have participated in the article preparation. Literature was searched by the first author who also wrote the first draft of this manuscript. Other authors critically revised the work, and all authors approved the final manuscript.

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