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Review article

Potential role of gut microbiota in major depressive disorder: A review

Mansoor Khaledi [a,b,1], Fatemeh Sameni [a,1], Abolfazl Gholipour [b], Shahnaz Shahrjerdi [c], Reza Golmohammadi [d], Hadi Esmaeili Gouvarchin Ghaleh [e], Behnam Poureslamfar [f], Jaber Hemmati [g], Niloofar Mobarezpour [h], Yaser Eshaghi Milasi [i], Fatemeh Rad [j], Mahtab Mehboodi [k], Parviz Owlia [l,*]

[a] Department of Microbiology, Faculty of Medicine, Shahed University, Tehran, Iran
[b] Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[c] Department of Physiology and Sports Pathology, Faculty of Sport Sciences, Arak University, Arak, Iran
[d] Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[e] Applied Virology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[f] Department of Biology, Faculty of Science, Yasouj University, Yasouj, Iran
[g] Department of Microbiology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[h] Reference Laboratory for Bovine Tuberculosis, Razi Vaccine and Serum Research Institute, Karaj, Iran
[i] Department of Clinical Biochemistry, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran
[j] Department of Microbiology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[k] Department of Microbiology and Virology, Kerman University of Medical Sciences, Kerman, Iran
[l] Molecular Microbiology Research Center, Faculty of Medicine, Shahed University, Tehran, Iran

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ABSTRACT

Interactions between the gut microbiota and host immunity are sophisticated, dynamic, and host-dependent. Scientists have recently conducted research showing that disturbances in the gut bacterial community can lead to a decrease in some metabolites and, consequently, to behaviors such as depression. Exposure to stressors dropped the relative abundance of bacteria in the genus *Bacteroides* while soaring the relative abundance of bacteria in the genus *Clostridium*, *Coprococcus*, *Dialister*, and Oscillibacter, *which* were also reduced in people with depression.

Microbiota and innate immunity are in a bilateral relationship. The gut microbiota has been shown to induce the synthesis of antimicrobial proteins such as catalysidins, type C lectins, and defensins. Probiotic bacteria can modulate depressive behavior through GABA signaling.

The gut microbiome produces essential metabolites such as neurotransmitters, tryptophan metabolites, and short-chain fatty acids (SCFAs) that can act on the CNS. In the case of dysbiosis, due to mucin changes, the ratio of intestinal-derived molecules may change and contribute to depression.

Psychotropics, including *Bifidobacterium longum* NCC3001, *Clostridium butyricum* CBM588, and *Lactobacillus acidophilus,* have mental health benefits, and can have a positive effect on the host-brain relationship, and have antidepressant effects.

* Corresponding author.
E-mail addresses: Parviz.owlia@gmail.com, owlia@shahed.ac.ir (P. Owlia).
[1] Please note that following authors considered as first author: Mansoor Khaledi, Fatemeh Sameni.

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This article reviews current studies on the association between gut microbiota dysbiosis and depression. Comprehensively, these findings could potentially lead to novel approaches to improving depressive symptoms via gut microbiota alterations, including probiotics, prebiotics, and fecal microbiota transplantation.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric illness with a global prevalence of 13.3 % [1]. This kind of disorder is a common and debilitating mental illness that is characterized by a depressed mood, appetite change, sleep disturbance, mental retardation or agitation, fatigue, guilt, loss of concentration, and suicidal ideation. Its worldwide prevalence is estimated at 4.4 % [2]. Depression is one of the most common mental disorders that affected approximately 280 million people in 2019 [3]. It includes periods in which a person's mood becomes very despondent, so the basic element is boredom [4]. Depression can also be associated with other disorders such as alcohol dependence, sleep, eating, and some personality disorders [5].

Consequently, depression is defined as a major progressive challenge in societies that imposes the most economic and social burden along with direct and indirect costs, high unemployment, low annual income, a high divorce rate, a declining quality of life, reduced job satisfaction, impaired personal communication, and even the emergence of suicidal thoughts [6,7].

According to a report from a survey of 30 countries, depression has a lifetime prevalence rate of about 10.8 % [8] and exerts a large clinical and social burden. Several hypotheses, including monoamine, subclinical inflammation, and the HPA, have been proposed to explain its underlying cause [9,10]. Another promising hypothesis is gut-brain axis dysfunction [11].

The gut microbiota affects both the digestive and the central nervous systems (CNS). Bacteria can produce neurotransmitters such as γ-aminobutyric acid (GABA), dopamine, and serotonin, which affect emotional states and sleep [12].

Studies on the intestinal microbiota in MDD are increasing. Although the results vary from one study to another, Naseri Afroui et al. seem to be the first reporters of a comprehensive microbiota profile of fecal samples from MDD patients. They analyzed the functional classification unit on 16S rRNA sequence data in 37 patients with MDD plus 18 controls and reported that, in contrast to the family Lachnospiraceae, the order Bacteroidales, genus Alistipes, and Oscillibacter increased compared to the observed group [13].

Subsequently, Jiang et al. examined 46 patients with MDD and 30 healthy controls and found that bacteria, protozoa, and actinobacteria increased while Firmicutes decreased in their patients compared with controls. At the family level, Enterobacteriaceae and Bacteroidaceae increased, while Ruminococcaceae decreased (Fig. 1) [14].

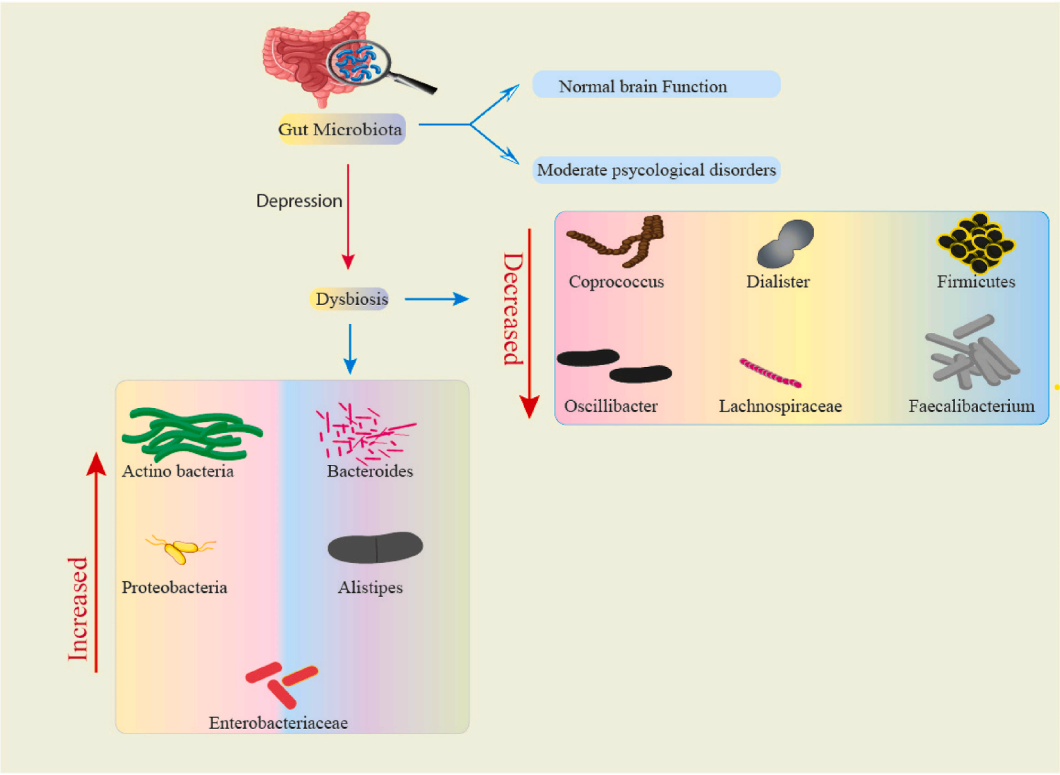

Fig. 1. The association between gut microbiota dysbiosis and depression.

Emerging evidence suggests a potential connection between the gut virome and MDD. Disturbances in the gut microbiome, including the gut virome, have been implicated in MDD [15]. In a mouse model of depression, notable disparities were observed in the gut virome profile between the depressed mice and the control group. Certain viral families were found to be more prevalent in the depressed mice, and alterations in neurotransmitters involved in tryptophan metabolism were also detected [16]. These findings hint at a possible association between the gut virome and MDD, but further investigation is required to gain a comprehensive understanding of the underlying mechanisms and potential therapeutic implications.

2. Gut microbiota and immunity

From an immunological point of view, microorganisms that are seen as pathogens will be detected and killed by the host immune system. However, most gut bacteria are non-pathogenic and have a symbiotic relationship with gut cells. Gut symbiotic bacteria mainly contribute to nutrient metabolism and intestine barrier function and inhibit the colonization of pathogenic microorganisms. The immune system is associated with healthy microbiota and is also aggressive against pathogenic microorganisms [17]. Furthermore, gut virome (including DNA and RNA viruses, bacteriophages, and retroviruses) have a parallel interaction with those bacteria in health and illness [18]. In fact, bacteriophages regulate bacterial populations by infecting and lysing bacteria, thus modulating the composition and diversity of the microbiota. In turn, the bacterial microbiota influences the replication and stability of viral populations [19].

The relationship between the intestinal microbiota and the immune system is complex, dynamic, and host-dependent. Disruption of the intestinal microbiota by various factors increases pathogenic infections as well as inflammatory diseases. Understanding the microbiota with pathogens and the immune system provides important insights into the pathogenesis of the disease, and manipulation of intestinal bacteria could be a new immunotherapeutic strategy for the prevention and treatment of inflammatory illnesses [20]. Notably, probiotics including *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *L. acidophilus*, and *Bifidobacterium* could improve intestinal disease through modulation of tight junctions [21]. The interaction of probiotic bacteria with intestinal epithelial cells induces a reduction in the response to various pro-inflammatory stimuli. The primary immune effects of the microbiota are decreased activity of nuclear factor kappa B (NF-κB), increased natural killer cells (NK) activity, dendritic cells (DCs) maturation, stimulation of cytokine production, and activation of antigen-presenting cells (APCs) found in Peyer's patches [22].

The microbiota is also important for the development of the mucosal immune system [23]. Preliminary studies show that the absence of commensal microbes Germ-Free (GF) is associated with profound intestinal defects and immune function. Intraepithelial lymphocytes (IELs) in GF mice are significantly higher than in normal animals; in fact, the secondary lymphatic organs grow less and thus give a relatively weak response to bacterial antigens. Commensal bacteria reduce the migration of phagocytes and activate the acquired immune system (T and B cells). Also, the gut virome has been implicated in immune tolerance by promoting the differentiation and activation of regulatory T cells. This helps to prevent excessive immune responses to harmless antigens, contributing to the maintenance of immune homeostasis [19]. Immunoglobulin (Ig) A antibodies are a mainstay of protective humoral immune defense at mucosal surfaces and substantially reduced in newborns and GF animals, which is rapidly repaired by microbial colonization [24]. For example, administration of *Lactobacillus casei* in mice increases IgA and cell production of mononuclear cells in Peyer's patches by interleukin-6 (IL-6). This suggests that *Lactobacillus* can enhance the immune response without inducing a T-dependent IgA response. Other research shows that prescribing *L. paracasei* increased $CD4^+$ T-DC interactions, lymphocyte proliferation, and secretion of cytokines IL-1β, IL-10, IL-12, interferon-gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) in Peyer's patches. Th17 cells are also absent in GF mice and can be induced by microbial colonization [25].

Molecular signals from the gut microbiome may modulate the function of brain cells [26]. Microglia is one of the main inherent immune cells in the CNS, which is effective in CNS immune defense and helps brain growth and homeostasis [27]. The microbiota contributes to microglia homeostasis [28]. GF mice have structure and function defects of the microglia and, therefore, have impaired CNS innate immune responses. Re-colonization with microbiota partially restored the properties of microglia. SCFAs regulate microbiota-derived bacterial fermentation products and microglia homeostasis. Accordingly, it was shown that the lack of the SCFA FFAR2 receptor in GF mice resulted in defective microglia. These findings suggest that host bacteria regulate the maturation and function of microglia [29]. Microbial signals can also regulate mucus secretion by signaling inflammation through nod-like receptor pyrin domain-containing protein 6 (NLRP6) to prevent autophagy, and mucus production is caused by goblet cells [30].

After gut damage, monocytes are stimulated by some microbiota members, such as *Proteus mirabilis*, to secrete NLRP3-dependent IL-1β, which causes intestinal inflammation [31]. The intestinal microbiota may also help modulate intestinal immunity. Stool microbiota transplantation contributing to antibiotic prescription may affect the efficacy and toxicity of immunotherapy through the microbiota [32]. Moreover, the gut microbiome adjusts tumor progression, and the manipulation of intestinal bacteria could be a new immunotherapy strategy [20].

Microbiota and innate immunity are in a bilateral relationship [17]. Evidence shows that a bacterial polysaccharide derived from commensal *Bacteroides fragillis* promotes the maturity of the immune system in mice, including the correction of systemic T cell deficiencies and Th1/Th2 imbalances in lymphatic tissues [33]. The specific gut viruses can vary depending on the individual and their gut virome composition. It has been found that phages with different Ig-like domains on their viral capsids, such as the T4 phage with Hoc proteins, can attach to mucin glycoproteins that are found on the mucous layer of the intestine. This attachment is facilitated by the interaction between the Ig-like proteins on the phages and the glycans displayed by the mucin. These phages, which are abundant and adhere to mucosal surfaces, play a crucial role in forming the innate immune barrier. By acting as an antimicrobial defense against luminal bacterial pathogens, they provide an initial line of protection for the host. Further research is needed to fully understand the impact of different gut viruses on innate immunity and human health [34].

Toll-like receptors (TLRs), NOD ligands, and metabolites that come from microbiomes have direct effects on immune cells and cells in the gut. They can also move to other tissues through the bloodstream and change the immune system [35]. *Fusobacterium nucleatum* changes the function of FomA and TLR2 in intestinal epithelial cells to affect extracellular vesicles and intrinsic immunity [36]. It has been shown that some gut viruses, like the Varicella zoster virus (VZV), can make human monocytes make IL-6 by activating TLR2 and CD14 [37]. Additionally, intestinal myofibroblasts have the ability to upregulate TLR2 expression after stimulation with lipopolysaccharides (LPS) or lipoteichoic acid (LTA) [38].

Microbiotas are a source of peptidoglycans that promote the innate immune system and increase the killing of pathogens by bone marrow-derived neutrophils. Common bacterial-derived peptidoglycans have been shown to stimulate NOD-1 receptors and increase their antibacterial activity [39]. The gut microbiota is essential for the normal growth and function of Foxp3+ T (Treg) regulatory cells. Nevertheless, the mechanism by which it is performed is still unclear [40]. Other studies show that the gut microbiota affects My-D88 signaling and activates it [41].

The gut microbiota also helps develop innate lymphoid cells (ILCs) [42]. In addition, the treatment of mice with antibiotics reduced NCR, ILC, and RORγt. The microbial flora causes the production of IL-22 in intestinal cells, which provides an innate immune defense in the mucosa [43].

In addition, the gut microbiota induces the production of antimicrobial proteins (AMPs) such as defensins, catalysidins, and type C lectins through the structural pattern receptor (PRR) as well as through their structural components and metabolites [44].

It has been indicated that healthy microbiota is a precursor for AMP production; *Bacteroides thetaiotaomicron* and *Lactobacillus innocua,* as well as bacteriophages*,* seem to be the most important species producing AMP [45,46]. *B. thetaiotaomicron* can activate defensins [47]. The gut microbiota can significantly regulate the function of both innate and acquired immune systems [48].

TLR signaling elicits DC-tolerant phenotypes, resulting in a T-cell-dominated immune response [49] *In vitro*, probiotic bacteria modulate the function of DCs, thereby inducing IL-10 regulatory T cells. DCs have a type C lectin receptor that detects and binds to MAMPs in the microbiota, including the common bacteria *L. casei* and *L. reuteri*, thus leading to Treg cell induction [50]. In addition, *Bifidobacterium infantis* stimulates DCs to stimulate Foxp3-regulated T cells and IL-10-secreting T cells [51]. Regulation of Th17 inflammatory cells by the microbiota prevents mucosal surface infections [52]. *Clostridium* IV and *Clostridium* XIVa have also been shown to affect the number and function of $Foxp3^{+}$ $CD4^{+}$ Treg cells [53].

Bacteroides, *Bifidobacterium*, *Lactobacillus*, and *Clostridium* ameliorate various immune defects in GF mice and regulate the expression of genes involved in intestinal growth, transmission, and protective immune functions [54].

Gut microbiota, especially gram-negative organisms such as *Bacteroids*, activate gut DCs, which stimulate plasma cells in the intestinal mucosa to express secretory IgA (sIgA). The sIgA, which can independently cover the gut microbiota, is mainly from the sIgA2 subclass and is more resistant to degradation by bacterial proteases. Commensal bacteria stimulate changes in the mucosal IgA class through a mechanism that is not well understood [55].

It is interesting to know that prescribing *Lactobacillus plantarum* protects well against viral infections like the mortal pneumonia virus, and it also reduces acute leptospirosis in mice through the myeloid cell mediating effect [56]. Laboratory mice receiving microbiota are less susceptible to infection with influenza virus and RSV (respiratory syncytial virus) and reduce pneumonia [57].

Several branches of bacteria are specifically involved in mucosal tolerance through iTreg induction [40]. *B. fragilis* has been shown to increase Treg function through polysaccharide coexisting factor A (PSA) and could also suppress Th17 inflammatory responses [58]. GF mice with colitis also induced IL-10 secretion by iTreg during microbial colonization with *B. fragilis* (PSA) and subsequently suppressed colitis. These results suggest that *B. fragilis* can mediate intestinal regulatory responses through a bacterial-associated molecule [59]. *Clostridium* spp. has been shown to increase the differentiation and frequency of the iTreg [60]. When GF or SPF animals were colonized with commensal Clostridia strains, their Th17 response decreased and Treg-induced IL-10 increased [61].

Commensals in the gut produce SCFAs such as butyrate, acetate, and propionate, which are immune-regulating metabolites [40]. Production of by-products such as lactate, SCFA, and other metabolites is due to bacterial fermentation. SCFA, which is the main source of energy for colonocytes, provides important protective immunological functions. Besides, commensal bacteria alter gut pH by producing SCFA, preventing the growth of opportunistic pathogens. For example, *Bifidobacterium* lowers gut pH during lactose fermentation, thus preventing the colonization of the pathogenic *Escherichia coli* [62]. An SCFA called butyrate, released by *Faecalibacterium prausnitzii*, maintains the Th17/Treg balance and inhibits IL-6 signal transducers. The STAT3/IL-17 pathway exerts significant anti-inflammatory effects and increases Foxp3 expression. Butyrate, derived from commensal bacteria, stimulates Treg cells in the intestinal tract by binding to transcription factors, inhibiting histone diestylase, and producing transforming growth factor beta (TGF-β) in IECs [63]. SCFA acetate, which is highly produced by *Bifidobacteria*, has anti-inflammatory properties in neutrophils. Acetate also stimulates the proliferation of Treg cells in the lamina propria and regulates intestinal homeostasis [62].

The microbiota directly affects the number of Kupffer cells (a type of resident macrophage in the liver) [64] and may be involved in the fertility and maturation of tissue-dwelling macrophage precursors [65].

A study showed that reducing *Alistipes*, *Desulfovibrio*, *Faecalibacterium*, *Lachnobacterium*, and *Oxalobacter* in individuals can negatively affect their health. The results showed that in aging, a decrease in *Bacteroides* levels and *Bacteroides/Firmicutes* ratio could be associated with abnormalities in host humoral immunity. Bacteria can stimulate the host's cellular and humoral immunity. This indicates the effect of the intestinal microbiota on the immune system, and aging can also negatively affect the quality and quantity of human gut microbiota. Therefore, homeostasis in intestinal microbes is important for maintaining the function of the immune system [66].

3. Combination of altered intestinal microbiota (dysbiosis) and depression

Scientists have recently conducted research showing that an imbalance in the gut bacteria can lead to a decrease in some metabolites and, consequently, to behaviors such as depression. These findings show that a healthy gut microbiota affects the normal functioning of the brain. It can also moderate psychological disorders associated with neurodevelopmental defects [67]. Treatment with *B. fragilis* also reduces neurodegenerative defects [68]. Exposure to stressors dropped the relative abundance of bacteria in the genus *Bacteroides,* whereas it soaring the relative abundance of bacteria in the genus *Clostridium* [69].

Living bacteria that have positive mental health benefits are known as "psychobiotics" [70]. *Lactobacillus* counts are low in people with stress [70]. Studies in mice have shown that treatment with *Blautia coccoides* diminishes anxiety levels [71]. In this case, the use of particular bacteria can be a promising way to restore a healthy microbiota and a more effective treatment of mood disorders.

Probiotics have a significant effect on improving depressive symptoms by increasing serotonin levels and reducing inflammation. They can be considered as possible alternative therapies to control and improve the function of brain reactions caused by depression [72]. High levels of homocysteine have also been shown to be associated with depression, and treatment with probiotics can lower homocysteine levels in humans [73,74]. Studies have shown that the probiotics *Bifidobacterium langum* and *Lactobacillus holoticus* can reduce anxiety in patients after 30 days [75]. *B. langum* also lowers cortisol levels [76]. One study found that *Bifidobacterium* had a similar effect to the antidepressant drug citalopram [77]. Two groups of bacteria, *Coprococcus* and *Dialister*, were also reduced in people with depression [78].

Decreased levels of *Acylibacter* in the gut are also linked to depression. The *oscillibacter* strain contains a major metabolite called valeric acid, which is a neurotransmitter homologue to GABA. Valeric acid has been shown to bind to the GABA receptors. In addition, the GABA neurotransmitter may be produced by gut bacteria. These studies suggest that bacteria that are involved in the production and metabolism of valeric acid may be associated with depression [79].

Studies in mice show that *C. butyricum* MIYAIRI modulates microglial activation and can affect depressive behaviors such as chronic social failure [80].

The gut microbiota increases oxytocin levels. Oxytocin also reduces anxiety and stress [81]. *Lactobacillus johnsonii* may also increase oxytocin, enhance and improve social behavior, and neurological diseases [81]. Interestingly, the loss of gut microbiota in early adolescence affects oxytocin signaling and reduces hypothalamic and vasopressin oxytocin levels in stressed mice [82]. *L. reuteri* increases oxytocin and decreases plasma corticosterone levels in mice [83].

Based on the results of research, the plenitude of *Faecalibacterium* can be negatively related to the severity of depression symptoms. The same relation was seen for the other four genera: *Clostridium* XIVa, *Streptococcus*, *Erysipelotrichaceae incertae sedis*, and *Veillonella*. Gender can be another influential factor in such results. On the other hand, the number of *Collinsella* in male patients with MDD was increased as a result of symptoms of depression severity. Therefore, *Collinsella* can be a useful indicator for the clinical management and treatment of MDD [84].

The gut microbiome produces essential metabolites such as neurotransmitters, tryptophan, and SCFA metabolites that can act on the CNS. In dysbiosis, which is caused by changes in mucin, intestinal-derived molecular ratios may change, affecting depression [85]. SCFAs have been shown to increase depressive-like behaviors in mice by inhibiting histone deacetylase (HDAC). For example, repeated injections of sodium butyrate in mice modulated microglia activation and were effective in LPS-induced depression [86]. In addition, tryptophan catabolites (TRYCATs) can play a role in the development of several neurological diseases, including major depression [87]. Recent studies show that *Lactobacillus* spp. can produce high levels of reactive oxygen species (ROS), which may play a role in depression by disrupting tryptophan-kynurenine metabolism. Kynurenine disrupts the balance of neurotransmitters and causes depression [88].

Iproniazid was the first drug used to treat depression in the 1950s. The selection of this drug was based on its euphoric effects in tuberculosis patients.

At the time, iproniazid could treat seizures but was used only in very specific cases, and these studies showed an association between antidepressants and iproniazid effects [89]. Isoniazid derivatives such as isocarboxazid, phenelzine, tranylcypromine, and the reversible inhibitor MAO-A, moclobemide, offer significant effects on refractory depression [90].

Epidemiological research has shown an association between the antidepressant effects of some antibiotics, such as beta-lactams, tetracyclines, and fluoroquinolones. Also, some antidepressants and antibiotics have shown synergistic effects against microorganisms such as *Corynebacterium urealyticum* [91].

In addition, the findings show that doxycycline can have antidepressant properties by preventing and reversing the oxidative and inflammatory changes in the brain caused by LPS in mice. Another example of the antibiotic D-cycloserine, which is involved in the treatment of *Mycobacterium tuberculosis*, has antidepressant effects [90].

Studies show that ketamine has antimicrobial activity against some bacterial species, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa*, and can even improve treatment-resistant depression [92,93].

4. Relationship between gut microbiota and MDD

The pathophysiology of MDD is very sophisticated and has various effects on different people, which can be divided accordingly:

1) increased inflammatory response involving increased peripheral levels of TNF-α, IL-6, C-reactive protein (CRP), and other acute inflammatory proteins [94].

2) Impaired regulation of the HPA axis [95].
3) Oxidative stress (OS), which results in an imbalance between ROS and systemic antioxidants, is detrimental to fats, proteins, and nucleic acids [96].
4) Disorders in cellular immunity [97].

These events cause damage to mitochondrial bioenergetics that is associated with mood disorders and chronic fatigue syndrome [98]. The events are due to an imbalance in the gut microbiota as well as disruption of the intestinal barrier.

The microbiota of people with MDD is remarkably different from that of healthy people, and the number of gut microbiota, such as the ratio of *Firmicutes*, *Actinobacteria*, and *Bacteroides,* has decreased. Furthermore, fecal transplantation with the microbiota of MDD people in germ-free mice has led to depressive-like behaviors related to the disruption of microbial genes and host metabolites [99]. It has also been shown that specific bacterial genera are associated with clinical phenotypes, which is a solution option for microbiota-based therapeutics.

Antibodies produced in response to LPS indicate the role of bacterial translocation in the pathophysiology of MDD [100]. The cells of the intestinal mucus membrane are connected by tight junctions, and, these connections create a barrier between gut bacteria and the interstitial cell in healthy conditions. Disruption of the integrity of mucosal barriers and tight junctions can lead bacteria to pass into the lamina propria, mesenteric lymph nodes, and peripheral blood. Translocation of Gram-negative bacteria and their products, such as LPS, to mesenteric lymph nodes and peripheral blood binds to TLR2,4, activates the immune system, and produces pre-inflammatory cytokines and ROS [101].

Changes in gut barrier function are due to dysbiosis and inflammatory responses that increase the permeability of intestinal mucus and the transfer of bacteria and their derivatives to the circulation [100]. Transmission of Gram-negative bacteria to the mesenteric glands and bloodstream is very important for pathogenic bacteria. This incident can promote an immune-inflammatory response. Gram-negative bacterial transmission is also associated with inflammatory responses by activating TLR2,4 with LPS, which ultimately leads to the stimulation of the immune response and ROS generation [102]. Bacterial lysosomes and mediators secreted by monocytes are among the inflammatory responses [103].

Transmission of Gram-negative bacteria from the gut is associated with increased ROS levels and secondary OS-induced autoimmune responses, including peroxide anti-low-density lipoprotein (LDL) antibodies and IgM produced by phosphatidyl inositol, malondialdehyde, azelaic acid, nitro-tryptophan, and nitro-tyrosin in people with MDD [104]. Proinflammatory cytokines can disrupt tight junctions and facilitate the transport of these metabolites [105]. LPS can also increase the expression of nitric oxide-inducing synthases that stimulate nitric oxide formation through macrophages during activation via IFN-γ [106].

Furthermore, LPS motivates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which activates NF-κB and produces inflammatory indicators such as peroxide, superoxide, and cyclooxygenase-2 [107]. In addition, microglial activation via LPS can cause ROS synthesis, which leads to the initiation of oxidative processes in proteins and proteolysis [108]. Animal studies have shown that LPS injection increases levels of malondialdehyde, nitrite, and nitrate, as well as decreases glutathione levels in the brain, which has been found in psychiatric disorders [109].

In addition, the use of antioxidants such as quercetin reduces LPS-induced OS levels [110]. OS also exacerbates the degradation of the integrity of the intestinal tight junction [111].

As a result, bacterial translocation may create conditions that increase the potential for an autoimmune response in depressed patients [112].

5. The pathophysiology of MDD

Due to the development of neuroscience and bioinformatics, the pathophysiology of MDD is improving. In general, there are four aspects to the pathophysiology of MDD, which will be described below. Brain abnormalities are caused by an imbalance of neurotransmitters that disrupts the neuronal pathway and disruption [113]. Also, the disorder in the HPA axis is mainly due to the disruption of negative feedback mechanisms [40]. In addition, immune system changes involve chronic inflammation [114], and gut-brain axis disruptions cause gastrointestinal disorders and dysbiosis [115].

5.1. The brain disorder

Neurotransmitters play an essential role in the brain, and consequently, mood and behavior, as well as neurotransmitter imbalance, are closely related to depressive disorder [42]. Monoaminergic neurotransmitters such as serotonin (5-HT), dopamine, and norepinephrine produce positive behaviors and happiness. There is a hypothesis that a low level of these neurotransmitters may cause depressive behaviors, and vice versa, increasing the level of these neurotransmitters may have antidepressant effects [116].

One study found that serotonin was slow-acting and only beneficial for several depressed patients, suggesting that there are other mechanisms in depressed patients [117]. Several studies show other neurotransmitters are also involved in depression, such as increased glutamine and acetylcholine, and decreased GABA has been proven in MDD patients [42,118].

The prefrontal cortex, amygdala, and hippocampus play an essential role in regulating stimulation, emotion, cognition, and stress responses. In depressed patients, the function of the prefrontal cortex and hippocampus is impaired, leading to increased amygdala activity [46].

Brain-derived neurotrophic factor (BDNF) is a neurogenesis regulator; reducing it increases the symptoms of depression and apoptosis in neurons. Long-term use of antidepressants increases BDNF, stimulates neurogenesis, reduces the death of hippocampal

neurons, and improves cognitive states and behaviors [40,119].

Studies have shown that in depressed patients, in addition to neurogenesis disruption, there are problems such as decreased neuronal flexibility and myelin dysfunction [113,120]. There is a new hypothesis that neuroplasticity disruption raises the symptoms of depression, which is caused by many risk factors, including decreased BDNF and an imbalance in neurotransmitters.

Antidepressant therapies focus on restoring neurotransmitter levels by increasing flexibility and diminishing neuronal apoptosis [121–123]. In addition to the molecular and cellular hypothesis, there is also the neural circuit hypothesis, which focuses on changes in how the brain works. This theory says that depression is caused by a disruption in the connection between certain brain cells [113, 124].

5.2. The HPA axis dysfunction

The HPA axis plays a significant role in stress responses, and disruption of this axis is one of the main causes of depression [125, 126]. Physiological and psychological stress activates the HPA axis and releases vasopressin (AVP) and corticotrophin-releasing factor (CRF) from the hypothalamus. AVP and CRF stimulate the posterior pituitary gland and release an adrenocorticotrophic hormone (ACTH). This makes more glucocorticoids (GC) and other adrenocortical hormones come out. Inhibition of AVP and CRF secretion by the hypothalamus causes negative feedback [127]; more than half of depressed patients have a disruption in HPA-negative feedback, and some depressed patients also develop hypercortisolemia [125,128].

There's a hypothesis that glucocorticoid (GR) receptors play a crucial role in HPA axis function in depression. Increasing GC reduces GR sensitivity. This is when antidepressant therapies escalate GR expression and improve negative feedback through GR [126, 128]. Studies have also shown that disruption of the HPA axis alters neurotransmitters [129], decreases BDNF [127], and impairs neuronal flexibility [113,130].

5.3. Immune system abnormalities

Inflammation and depression are closely related, and in depressed patients, there's a disorder of the immune system and chronic inflammation [58]. In depression, proinflammatory cytokines such as IL-6 and TNF-α increase, and anti-inflammatory cytokines such as IL-10 and TGF-β are suppressed. This rise in proinflammatory cytokines has effects like blocking negative feedback on the HPA axis, making the blood-brain barrier more permeable, messing up the glutamatergic pathway, and lowering the production of 5-HT, all of which ultimately lead to depression [59,60].

In addition to peripheral inflammation, neuroinflammation also causes depression. Thus, pro-inflammatory cytokines produced by microglia have adverse effects on the CNS [130], and inflammasome function induces neuroinflammation [61]. Neuroglial cells also regulate immunity in the CNS and neuronal flexibility [130].

5.4. Gut-brain axis dysfunction

Patients with depressive disorder may experience disruption of the gut-brain axis, which has implications for appetite, metabolism, and gastrointestinal function [14,131]. These patients usually have several disorders simultaneously, such as immunodeficiency and gut-brain axis dysfunction. In addition, these disorders interact with each other in such a way that long-term stress decreases 5-HT levels in the brain. The synthesis and release of 5-HT are affected by several factors, such as the HPA axis, the gut-brain axis, and the immune system, and 5-HT also affects the function of these pathways [40,132].

The gut-brain axis transmits messages and establishes bidirectional communication between the brain and the intestine through pathways such as neurons, the HPA axis, and the immune system [62].

Numerous effects, such as stress and illness, are detrimental to these pathways, which in turn cause dysfunction of this axis and depression [63]. Further studies on gut microbiota cause more focus on the effects of the gut on the gut-brain axis [133]. Numerous systems in the body, such as neuronal, immune, hormonal, and metabolic, are influenced by the gut-brain axis. Also, changes in the gut-brain axis have several effects on moods and behaviors that have the therapeutic option of using this axis as one of the treatments for depression and brain disorders [65,66,134].

In the gut-brain axis, the gut microbiota plays an important role in behaviors and mental diseases [70]. In addition, the gut microbiota is involved in HPA axis maturation [67], immune function [68], synthesis of neurotransmitters [67,132], neurogenesis [69], and myelin formation [135].

5.5. The connection, between the gut microbiota and mental health

The correlation, between gut microbiota and mental health pertains to how the microorganisms residing in our system impact our mental well being. Our gut is home to bacteria, viruses and fungi collectively referred to as gut microbiota. These microorganisms have a role, in digestion, immune function and the absorption of nutrients [136].

New studies have indicated that the gut microbiota plays a role, in our abilities and emotional well being [137]. This is due, to the network of nerves, hormones and biochemicals connecting the gut and the brain, commonly known as the gut brain axis [138]. Through this connection the gut microbiota has the power to impact neurotransmitter production and regulation including serotonin and dopamine which greatly influence our emotions and behavior [139].

Imbalances, in the gut microbiota, which refers to a state known as dysbiosis have been linked to a range of health conditions such

as anxiety, depression and even autism. Several studies have discovered that individuals with these disorders exhibit compositions of gut microbiota compared to those who're in good health [140]. Furthermore research has demonstrated that making changes, to the gut microbiota by using probiotics, prebiotics and adjusting ones diet can potentially improve symptoms related to well being [141].

One possible explanation for the Relationship between gut microbiota and mental health is the role of inflammation. Dysbiosis in the gut can lead to increased inflammation, which has been Relationshiped to the development of mental health disorders [142]. The gut microbiota also influences the production of other inflammatory markers, such as cytokines, which can impact brain function and behavior [143].

Moreover it's worth noting that the gut microbiota can also be influenced by stress and various psychological factors. Research has indicated that persistent stress has the potential to disturb the equilibrium of the gut microbiota resulting in dysbiosis which could potentially play a role, in health disorders [144].

The connection, between the gut microbiota and mental health has gained attention in times [145]. Studies have revealed that the gut microbiota also interacts with the brain through a pathway known as the gut brain axis, impacting brain function and behavior bidirectionally [6].

A comprehensive analysis of studies examined the variations, in the composition of gut microbiota among individuals diagnosed with major depressive disorder (MDD) bipolar disorder (BD) and schizophrenia in comparison to individuals, without any mental health conditions [145]. While this review did not find strong evidence for differences in the number or distribution of bacteria in those with mental disorders compared to controls, it highlighted the complexity of studying the gut microbiota in the context of mental health. Another study explored the dynamic changes of the intestinal flora in patients with irritable bowel syndrome (IBS) combined with anxiety and depression after oral administration of enterobacteria capsules [146]. The findings suggested that fecal microbiota transplantation (FMT) therapy has the potential to alleviate clinical symptoms and restore the intestinal micro-ecology in patients with IBS and comorbid anxiety and depression. Furthermore, a review discussed the relationship between the gut microbiome and depression, emphasizing the potential of gut microbiota in influencing mood-related behaviors with substantial clinical implications [147]. Studying the interaction, between gut microbiota and depression sheds light on research areas that aid our understanding of how the gut microbiota affects mood related behaviors. Existing literature indicates a connection between gut microbiota and overall well being potentially influencing the development of disorders. While we are still unraveling the underlying mechanisms, these findings open up avenues for interventions and treatment strategies, for health concerns.

6. Treatment of MDD

6.1. Probiotics

Probiotics are supplements that contain live microorganisms found in food products, including dairy products and fermented vegetables [71]. Probiotics include bacterial species such as *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Bacillus*, and *E. coli*, which are the most common [72]. Probiotics play a role in maintaining gastrointestinal health by improving mucosal barrier function and having a significant effect on modulating the mucosal immune system and intestinal permeability [148]. The benefits of probiotics often do not include all of their species; for example, the synthesis of some vitamins, the hydrolysis of bile salts, and the protection of intestinal integrity by certain species. Probiotics affect the function of the immune system and produce cytokines. They reduce inflammation, stimulate sIgA, regulate T cell proliferation, and improve immune function [72,74]. In many diseases, including hypertension and cardiovascular diseases, the use of probiotics reduces the symptoms associated with these diseases and, in part, improves them [73]. Psychotropics are defined as probiotic strains that, if taken in the right amounts, have mental health benefits, and can have a positive effect on the host-brain relationship, and have antidepressant effects (Table 1) [72]. Probiotic strains can affect perception and thinking; taking probiotics increases the levels of neurotransmitters such as GABA and serotonin in depression [71]. Probiotic supplements may be an adjunct treatment for major depression and reduce the rate of depression in MDD patients [71,149–151]. Patients

Table 1
The potential benefits of different bacterial species in enhancing depression.

Bacteria	Improve depressive symptoms	References
Bacillus licheniformis capsules	+	[148]
Bifidobacterium	+	[148]
Lactobacillus capsules	+	[148]
Enterococcus	+	[148]
Lactobacillus helveticus R0052 (dose 10 *10^9 CFU)	+	[76]
Bifidobacterium longum R0175 (dose of 10 *10^9 CFU)	+	[76]
Lactobacillus helveticus R0052 (dose 3*10^9 CFU)	–	[76]
Bifidobacterium longum R0175 (dose 3*10^9 CFU)	–	[76]
Bifidobacterium longum NCC3001	–	[76]
Lactobacillus helvetivus IDCC3801	–	[76]
Bifidobacterium coagulans MTCC5856	+	[76]
Clostridum butricum CBM588	+	[76]
Lactobacillus acidophylus	+	[76]
Lactobacillus casei	+	[76]
Bifidobacterium bifidum	+	[76]

with depression have considerable differences in the composition of the gut microbiota compared to those without depression, and increased probiotic gut microbiota may affect mood and other factors. Probiotics such as *Bacillus licheniformis* capsules, *Bifidobacterium*, *Lactobacillus* capsules, and *Enterococcus* can be symptoms of depression, and they improve the sad mood (Fig. 2) [148]. According to many different studies, *Lactobacillus helveticus* R0052 and *B. longum* R0175 with a "CFU dose of 10×10^{9} in patients with MDD improve depression, while the same species with a "lower dose of 3×10^{9}" does not have a significant effect on depression. Other species of *B. longum* NCC3001 and *L. helveticus* IDCC3801 do not have beneficial antidepressant effects. *Bacillus coagulans* (MTCC 5856) and *Clostridum butricum* (CBM 588) have a significant reduction in depressive symptoms. On the other hand, species such as *L. acidophylus, L. casei*, and *Bifidobacterium bifidum* have appropriate and significant effects on improving depression (Table 1) [76].

6.2. Prebiotics

Foods are indigestible and fermented into SCFAs. They stimulate the growth and activity of intestinal microbiota and affect the function of microbiomes [78]. Prebiotics are fermented substances that alter the composition or activity of the microbiota of the gastrointestinal tract. In addition to the large intestine, these prebiotics can also have benefits in the mouth and urogenital tract. The ability of prebiotics to change the composition of the intestinal microbiota toward enrichment with microbial groups is their most prominent feature. Prebiotics can be used as an energy source in fermentation processes [79]. Prebiotics exist in two ways: 1. They are naturally present in plants. 2. They are made artificially from polysaccharides after the enzyme is digested. Natural prebiotics are divided into 3 main types: GOS "Galacto-oligosaccharides", FOS "Fructo-oligosaccharides", and SOS "Soy oligosaccharides". The most common synthetic prebiotics are lactosacrosis, lactulose, isomalto-oligosaccharide, glucooligosaccharides, and xylooligosaccharides. The most important prebiotics are fructooligosaccharides, inulin, galactooligosaccharides, and lactulose [80]. The role of oligo-fructose (OF) in the prevention of *Clostridium difficile* diarrhea has been proven. Also, GOS and FOS can be used in irritable bowel syndrome (IBS) or lactulose and OF in constipation. Inulin is a prebiotic dietary fiber that affects the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*. These bacteria have an effect on mood in the treatment of IBS patients [81,152]. In obese people, one of the biological factors involved in behavioral disorders is the intestinal microbiota, which is composed of several microorganisms some prebiotics affects the function of these microorganisms; and gut microbiota affect brain function and behavior in various ways [152]. FOS, GOS, or a combination of these are beneficial for behavioral performance during anxiety and depression. Prebiotics affect the growth of probiotics, including *Bifidobacterium* and *Lactobacillus*. Some species, such as *B. bifidum* and *L. acidophilus,* are useful in the treatment of depression, and prebiotics play a useful and effective role in the microbiota-brain-intestinal axis [82].

6.3. Fecal microbiota transplantation (FMT)

It is a method in which the feces of healthy donors are transferred to a sick person, and the use of this method dates back to the fourth century in China. It is a beneficial method to improve the function of the intestinal microbiota and is used in the treatment of gastrointestinal diseases such as food poisoning and severe diarrhea [83]. FMT A suitable alternative treatment is used to treat recurrent *C. difficile* infection (rCDI) [153]. FMT has been performed through the upper or lower gastrointestinal tract, which includes

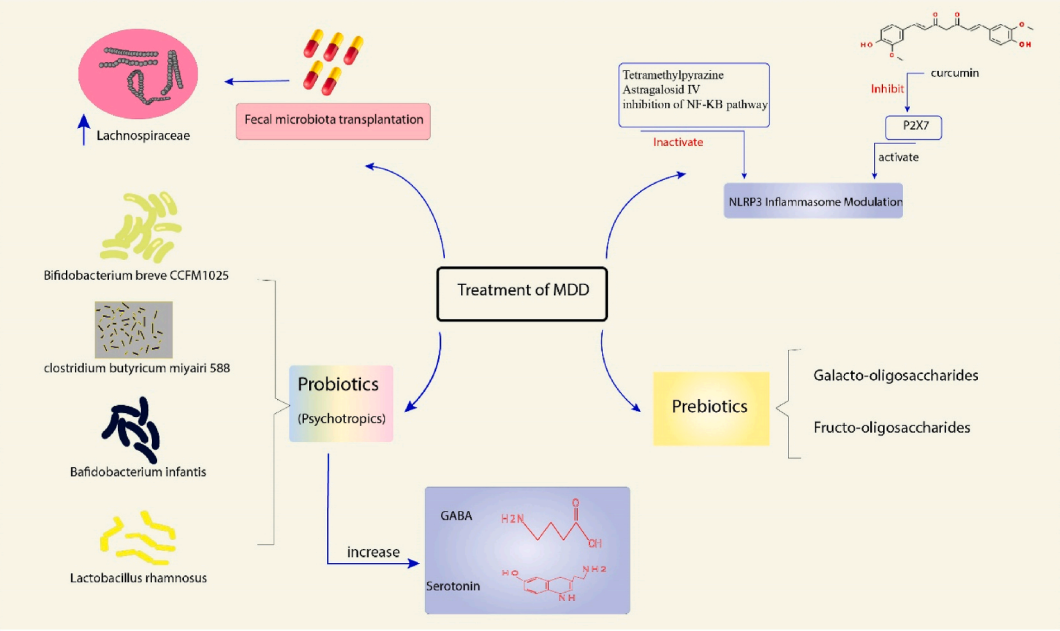

Fig. 2. The methods based on gut microbiota for treatment of MDD.

various methods such as colonoscopy, capsule swallowing, enema, and the use of a feeding tube. The best FMT method is colonoscopy [154,155]. FMT is effective in treating diseases such as metabolic syndrome, Crohn's disease, insulin sensitivity, *C. difficile* infection, Parkinson's, multiple sclerosis, psoriasis, anorexia nervosa, and Alzheimer's. Before FMT, the donor should be screened for viruses such as HIV, hepatitis A, B, C, and autoimmune diseases, and the donor should not have used alcohol, drugs, or drugs that affect the gut microbiota [156,157]. FMT can be effective in relieving some psychiatric disorders, including MDD (Table 2) [158,159]. Increasing the proportion of pathogenic bacteria upsets the balance of the intestinal microbiota and may be effective in causing some neurological diseases. The use of probiotics, prebiotics, psychotropics, and FMT has been implicated in the modulation of gut microbiota and helps to improve psychiatric disorders [160]. The study reported that the transfer of stool from a depressed human to antimicrobial mice induced depressive behaviors in mice [161]. Other experiments showed that mice lacking commensal germs altered brain function and related disorders and that exposure to probiotics and FMTs alleviated anxiety-like behaviors and depression [83]. In another experiment, FMT transferred feces from mice on a high-fat diet to antimicrobial mice, causing the recipient mice to be psychologically affected and lack social interaction [162]. Performing FMT from healthy donors improves several neurological disorders, and it was found that FMT is useful for relieving depression in an elderly patient. So before treatment with FMT, *Lachnospiraceae* bacteria were few, but after an increase in FMT, *Lachnospiraceae* break down carbohydrates into SCFA. If the number of species of this bacterium is small, it reduces SCFAs. As a result, it reduces 5-HT, which is a neurotransmitter in depression, and exacerbates depressive symptoms (Table 2) [163].

6.4. NLRP3 inflammasome modulation

NLRP3 is an important signaling molecule that plays a significant role in causing inflammation and is significant in the pathogenesis of various physical and mental disorders of the CNS, including depression [154,167]. Depressive disorder is a psychiatric disorder in which various environmental factors, including inflammation, affect the process and how it affects people [168]. NLRP3 inflammation is involved in neuroinflammation and neurological disorders such as depression (Table 3) [169,170]. In a laboratory study in LPS-induced mice, NLRP3 inflammation was stimulated,and mice exhibited depressive behaviors using the traditional drug Mahuang-Fuzi-Xixin (MFX) to exert antidepressant effects on mice [170]. Cytokines produced through environmental inflammation can cross the blood-brain barrier, activate the afferent nerves, and contribute to depressive disorders [168,171].

NLRP3 acts as a mediator in depression. The neuroinflammation pathway is involved in MDD, so people with MDD have more caspase-1, NLRP3 mRNA, and NLRP3 protein in their peripheral blood cells than people who aren't depressed [170,172].

In a laboratory study in mice with chronic conditions, they used dexamethasone, which activated NF-κB in HAPI cells (the mouse microglia cell line), which is the most significant factor in the NLRP3 inflammatory pathway. Increased glucocorticoid concentration is the main factor activating NLRP3 in microglia and neuritis [169]. Hesperidin was used in another study on rats that had chronic unpredictable mild stress (CUMS). It stops NLRP3 inflammation and plays a part in the activation of microglia in the prefrontal cortex of mice with CUMS conditions (Table 3) [173].

The use of antidepressants in human and mouse samples helps reduce the expression of inflammatory pathways and proinflammatory cytokines. The inhibitory effect of various antidepressants on the function of inflammatory cytokines in patients has been investigated through cell cultures and laboratory models [174,175]. In addition, studies have shown that the P2X7 receptor signal alters depressive behaviors because P2X7 activates NLRP3, which affects depression [176,177]. Curcumin is an anti-inflammatory drug. an experiment in CUMS-induced mice prevented P2X7-induced NLRP3 inflammation and prevented the conversion of pro-IL-1 to IL-1 because the inflammatory cytokine IL-1 plays an important role in causing depressive-like behaviors. Indolamine 2 and 3 dioxygenase has been shown in clinical studies on mice to stop proinflammatory cytokines and get rid of depressive symptoms [177]. CUMS-induced mice, under the influence of inflammatory cytokines and stressful conditions, can activate NLRP3 and induce depressive-like behavior in mice. Tetramethylpyrazine (TMP) was used to modulate NLRP3 levels, which inhibited the TLR4/NF-kB/NLRP3 signaling pathway, reduced IL-1β, IL-6, and TNF-α levels, and exerted its antidepressant effects in CUMS-induced mice [154].

Senegenin (SEN) is an antidepressant that works in the laboratory model of CUMS. Indolamine 2 and 3 dioxygenase has been shown in clinical studies on mice to stop proinflammatory cytokines and get rid of depressive symptoms [178]. In the rat model under CUMS conditions, administration of Prilla aldehyde (PAH) and fluoxetine (FLU) reduced the level of proinflammatory cytokines via the

Table 2
The potential impact of FMT on depressive disorders.

Experiment	Result	Reference
Transfer of stool from depressed humans to antimicrobial mice	Develops depressive-like behavior	[163]
Stool transfer from fatty diet mice to antimicrobial mice	Behavior changes and decrease in social interaction behaviors	[162]
Antimicrobial commensal mice with impaired brain function exposed to probiotics and FMT	Modify and improve depressive behaviors	[163]
FMT in the chronic unpredictable mild stress rat model	Ameliorate depression-like behaviors and neuroinflammation	[164]
FMT from healthy donors to alcohol-induced depression mice	Alleviate depression-like behaviors	[165]
FMT from healthy donors to patient with MDD	Improve MDD and chronic constipation	[166]

FMT: Fecal microbiota transplantation, MDD: Major depressive disorder.

Table 3
The function of NLRP3 in the pathogenesis of depressive disorders.

Experiment		Result	Reference
Fu et al. (2019)	Modulation of NLRP3 by use of TMP (in CUMS-induced mice)	Improve depression	[154]
Tian et al. (2021)	Inhibition of NLRP3 inflammatory activation (in mice)	Improving the function of depressive-like behavior	[167]
Xie et al. (2020)	Inhibition of NLRP3 inflammation by use of hesperidin with CUMS (in rats)	Antidepressant effects	[173]
Li et al. (2019)	Inhibition of NLRP3 pathway activation, by use of SEN (in CUMS-induced mice)	Antidepressant effect	[158]
Song et al. (2018)	Reduce the level of inflammatory cytokines by administration of PHA and FLU (in rats with CUMS)	Antidepressant effect	[179]
Song et al. (2018)	Inactivate NF-κB, GSK3β, and NLRP3 inflammation by use of AS IV (in model of RRS mice)	Controls depression	[180]
Wang et al. (2020)	Inhibition of the NF-κB pathway, modulation of NLRP3 inflammation by use of TCA and FLU (in mice with CUMS)	Antidepressant effect	[171]
Feng et al. (2019)	Induction of microglia neuritis by use of dexamethasone (in mice under chronic stress)	Induction of depression	[169]
Jing et al. (2019)	Stimulation of NLRP3 inflammation, use of MFX drug (in mice)	Antidepressant effect	[170]
Zhang et al. (2019)	Inhibition of NLRP3 inflammation induced by P2X7 activity, use of curcumin (in CUMS-induced mice)	Improving the function of depressive-like behavior	[177]

NLRP3: Nod-like receptor protein 3, TMP: Tetramethylpyrazine, CUMS: Chronic unpredictable mild stress, SEN: Senegenin, PHA: Prilla aldehyde, FLU: Fluoxetine, NF-κB: Nuclear factor kappa B, GSK3β: Glycogen synthase kinase-3 beta, AS IV: Astragaloside IV, RRS: Repeated restraint stress, TCA: trans-Cinnamaldehyde, MFX: Mahuang-Fuzi-Xixin.

TXNIP/TRX/NLRP3 pathway in the rat hippocampus and investigated the antidepressant effects [179]. Astragaloside IV (AS-IV) has an anti-inflammatory effect and inhibits neuroinflammation by modulating the inflammatory pathways PPARγ, NF-kB, and NLRP3. In the repeated restraint stress (RRS) mouse model, AS-IV showed that it lowered the levels of inflammatory cytokines like IL-1β and TNF-α while increasing the levels of PPARγ. It also turned off NF-κB, GSK3β, and NLRP3 inflammation. On the other hand, AS-IV is effective in mice in which the production of inflammatory cytokines is induced by LPS, modulates the expression of NLRP3, and reduces depression [180].

TCA (*trans*-cinnamaldehyde) has an anti-inflammatory effect by inhibiting the NF-κB pathway and NLRP3 inactivation. In a study with CUMS mice, TCA combined with FLU blocked the NF-κB pathway, which in turn lowered NLRP3-induced inflammation in the rat hippocampus and forehead. This also changed NLRP3 and kept depression in check [171].

7. Conclusion

The relationship between the brain and the gut is bilateral. As the brain regulates gut function, gut microbiota can also affect mental activity. The gut microbiota exerts many functions by producing metabolites and stimulating the production of various hormones. As a result, it acts on the hypothalamus, amygdala, and hippocampus.

Depression is one of the leading causes of disability, morbidity, and mortality worldwide, and the intestinal microbiota is involved in its pathogenesis. Although the underlying mechanism of this relationship is unclear, it may be involved in modulating the release and efficiency of monoamine neurotransmitters, changes in HPA activity and function, activation of inflammatory and immune responses, and regulation of BDNF expression.

Limited human studies on depression and gut microbiota report specific findings of depression about the microbiota proportion, but studies aimed at determining the role of the gut microbiome in mental health. Depression has been shown to strongly link microbes in the gastrointestinal tract and their effects. It examines the way people think and how the gut-brain axis functions as a basic pathway, taking into account the management of several psychological issues and psychiatric illnesses.

As a result, the gut microbiota affects many aspects of human functioning. It is not unexpected that mood-related behaviors should be included. Depression is characterized by the withdrawal of adaptive behavior from a harmful and uncontrollable stimulus. This depressive behavior can have benefits for the depressed person. Therefore, the involvement of such an essential component of an individual's physiology as the gut microbiota in this process is not unexpected. Despite this, tracing the pathways through which the gut microbiota is involved in mood-related behaviors remains a major challenge for researchers, with significant clinical potential outcomes for people experiencing MDD or depressive-related disorders.

Also, studies evaluating depressed patients who are not taking medication and are active in a depressed state may help to address the potentially distorting effects of antidepressants. The strong evidence gathered in this study suggests that treatment with probiotics may improve MDD-related symptoms by increasing the availability of serotonin or decreasing levels of inflammatory markers. The potential of using probiotics as a treatment for MDD can have a major impact on those seeking antidepressant therapy by reducing the side effects associated with conventional antidepressants. Further research is needed to determine the effectiveness of probiotics in reducing depressive symptoms, as well as the ideal duration of treatment, dose, and probiotic strain to achieve health efficacy.

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Mansoor Khaledi: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **Fatemeh Sameni:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Data curation. **Abolfazl Gholipour:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Shahnaz Shahrjerdi:** Writing – review & editing, Writing – original draft, Visualization, Data curation. **Reza Golmohammadi:** Writing – review & editing, Writing – original draft, Validation, Software, Investigation. **Hadi Esmaeili Gouvarchin Ghaleh:** Writing – review & editing, Writing – original draft, Validation. **Behnam Poureslamfar:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Jaber Hemmati:** Writing – review & editing, Writing – original draft, Validation. **Niloofar Mobarezpour:** Writing – review & editing, Writing – original draft, Validation. **Yaser Eshaghi Milasi:** Writing – review & editing, Writing – original draft, Validation. **Fatemeh Rad:** Writing – review & editing, Writing – original draft, Validation. **Mahtab Mehboodi:** Writing – review & editing, Writing – original draft, Validation. **Parviz Owlia:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Data curation, Conceptualization.

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