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Review Article

Assistance of Gut Microbiota in Depression

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Abstract

The association between gut microbiota and mental health is a relatively new research topic that has gained traction in recent years. Depression is a serious mental illness and a leading cause of disability, morbidity, and mortality worldwide. Based on the WHO reports, there are approximately 350 million people affected by depression globally. Currently available treatments can temporarily alleviate the symptoms of depressive illness, but these management plans are unable to completely reverse the multifactorial pathology of depression, and the antidepressant medications may produce side effects and adverse drug reactions which may turn down the quality of life of patients. Research has shown that the gut microflora interacts with the brain through various mechanisms, and this leads to the recognition of the microbiome in managing mental health. By unveiling the complexities involved in this area can help to develop novel strategies to treat the depressed patients and to prevent the public from falling to depressive disorder.

Keywords: Gut microbiome, depression, neurotransmitters

INTRODUCTION:

The symbiotic association between gut microbes and humans has always piqued the interest of scientists since it provides insight into the genesis of numerous diseases. The gut ecosystem has evolved to contain a diverse population of microorganisms including yeasts, archaea, parasites, helminths, viruses, and protozoa, but the bacterial population is currently the most well characterized. The composition of the bacteria that inhabit our GI tract throughout our adult life is established early in our first few years of life and at this early-life stage they are particularly sensitive to manipulation by a number of environmental factors including mode of delivery (vaginal or C-section), whether we are breastfed or bottle-fed, diet, medication (in particular antibiotic medication), and exposure to viral or bacterial infections and stress and eventually leads to mood disorders like anxiety and depression with progressing age^[1]. In humans, gut microbes play an important role in nutrition (the breakdown of indigestible polysaccharides and the synthesis of vitamins), defense against dangerous pathogens, metabolism, physiology, and immunological function^[2,3]. Individual genetics, growth and development, and geographic location all influ-

ence the composition of one's gut microbiota^[4]. Dysbiosis and gut inflammation have been linked to numerous mental illnesses, including anxiety and depression, both of which are prevalent today^[5]. Depression is a widespread mood disorder that affects over 264 million people globally^[6]. Severe depressive symptoms were associated with higher rates of chronic disease, increased health-care consumption, and serious difficulties at work, at home, and in social activities^[7].

The central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamic pituitary adrenal (HPA) axis are all part of the complex bidirectional gut brain axis (GBA). Microbiota can interact with GBA through various mechanism. Environmental influences, such as emotion or stress, can stimulate the CNS and, in particular, the HPA axis. HPA is finalized to release cortisol and is triggered by a complicated interaction between the limbic system's amygdala (AMG), hippocampus (HIPPO), and hypothalamus (HYP). Corticotropin-releasing factor (CRF) secretion from the hypothalamus drives adrenocorticotrophic hormone (ACTH) secretion from the pituitary gland, which leads to cortisol

release from the adrenal glands. In parallel, the central nervous system communicates with different intestinal targets such as the enteric nervous system (ENS), muscular layers, and gut mucosa via both afferent and efferent autonomic pathways (SNA), regulating motility, immunity, permeability, and mucus secretion. The enteric microbiota interacts with these intestinal targets in a bidirectional manner, influencing gastrointestinal functions while also being modulated by brain-gut interactions [8]. At present most of the studies regarding microbes in human focus on gut microbes, as it has the highest density and number of bacteria, with majority of data coming from fecal samples and a lesser degree's mucosal biopsies. Fresh fecal samples are relatively easy to obtain, but the information obtained from these samples does not represent the entire picture within the gut [9,10].

NEUROTRANSMITTERS IN DEPRESSION

The three main monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) in the brain seem to be associated with certain symptoms of major depressive disorder [11]. Alteration of gamma-Aminobutyric acid (GABA) level can also lead to depressive disorder [12].

DOPAMINE AND GUT MICROBES

Dopamine (DA), a key neurotransmitter in the central and peripheral nervous systems, is involved in several biological functions and regulates cognitive activities like decision making, attention, memory, motivation, reward, locomotor activity, neuroendocrine regulation, and ingestion of water and food. Dopaminergic signaling dysfunction can result in a variety of mental health issues [13-15]. The major neurotransmitter the mesocorticolimbic circuit is DA and this circuit is influenced by changes in the makeup of gut microbes [16].

DA is transported from the ventral tegmental area (VTA) to the nucleus accumbens (nAcc) and amygdala via the mesolimbic pathway. The nAcc is in the ventral medial portion of the striatum and is thought to be involved in reward, desire, and the placebo effect. The limbic system's major component, the amygdala, is related with emotion. Many theories have been proposed implying that the mesolimbic route is involved in diseases such as addiction and depression, based on the nature of the cognitive sensations coupled with this pathway. The VTA is connected to the frontal cortex by the mesocortical pathway, which is closely linked to the mesolimbic pathway. This pathway is thought to act irregularly in people with neuropsychiatric illnesses like schizophrenia [17]. In the human body, the gut synthesizes more than 50% of the dopamine [18]. Dopamine synthesis has been found in *Staphylococcus* present in the human intestine, which can take up the precursor L-3,4-dihydroxyphenylalanine (L-DOPA) and convert it to dopamine using the staphylococcal aromatic amino acid decarboxylase (SadA) produced by these bacteria [19]. There is evidence suggesting that the gut microbiota can cause changes at the catecholaminergic level in the brain. This is vividly observed in germ free animals, which showed a decrease in the amino acid tyrosine (essential amino acid for the synthesis of noradrenaline and dopamine) when compared to recolonized germ-free mice, which induced an increase in the brain DA levels [20].

NOREPINEPHRINE AND GUT MICROBES

Norepinephrine (NE) also called as noradrenaline, a neurotransmitter found in both peripheral and central nervous systems. This catecholamine is synthesized through various intermediate steps, (l-tyrosine to nor adrenaline then to its methylated form adrenaline) [21]. Norepinephrine has been shown to play a role in a person's mood and ability to concentrate. Low levels of norepinephrine may lead to condi-

tions such as depression [22]. In individuals with depressive disorder, there is a deficiency of norepinephrine and dopamine in their brains [23]. Invitro studies with gut microbes like *Bacillus mycoides*, *Bacillus subtilis*, *Proteus vulgaris*, *Serratia marcescens* and *Escherichia coli* (K-12) etc. had shown norepinephrine in their biomass. It has not been confirmed that human gut microbiota has a prominent role is a regulating norepinephrine, but emerging body of science suggests link between the gut microbes and epinephrine [24]. A study using germ free mice found that mice without bacteria have substantially reduced levels of norepinephrine in the cecal lumen and tissue [25].

NE is released via activation of central adrenoceptor β_3 (Adrb3), while heat killed *Enterococcus faecalis* (EC-12)-treated male mice expressed higher Adrb3 in the prefrontal cortex compared with control group mice [26,27]. In -synuclein mutant mice, the norepinephrine depleting toxin DSP-4 and LPS changed the gut microbiome and caused neurotoxicity [28]. In a study conducted using mice, the neurotransmitters like norepinephrine, 5-Hydroxyindol acetic acid (5H1AA) -main metabolite of serotonin and 5-HT were significantly reduced in depressed mice when compared to control mice [29]. Maternal stress rats treated with the probiotic exhibit a normalization of the peripheral immune response, a reversal of behavioral deficits, and a restoration of basal NA concentrations in the pons area of the brainstem [30].

SEROTONIN AND GUT MICROBES

The gut-brain axis allows the bidirectional communication between CNS and gastrointestinal tract. Serotonin (5-hydroxytryptamine, 5-HT) functions as a key neurotransmitter at both terminals of this network. Gut microbes can metabolize essential amino acid tryptophan as a precursor for the synthesis of serotonin [31]. More than 90 % of serotonin is synthesized in the gut by specialized endocrine cells, called enterochromaffin cells (ECs), as well as mucosal mast cells and myenteric neurons [32]. In the intestinal microbial community, tryptophan decarboxylases play a role in increasing the ability of microbes to extract tryptophan from the diet by converting it into tryptophan amine, thus regulating mood and behavior by reducing the production of 5-HT in the brain [33]. In MDD patients, serotonin production is decreased. One of the most common objectives in treating depression is to increase 5-HT in synaptic cleft [34]. *Lactobacillus helveticus* NS8's antidepressant effect was related to restored hippocampal 5-HT and nor epinephrine levels in rats subjected to prolonged restraint stress [35]. Despite the diversity of the gut microbiota, a single microbial strain, *Lactobacillus reuteri*, has been shown to protect against depressive-like behaviors generated by chronic social defeat stress in mice due to improved gut microbiota and serotonin metabolism [36].

GABA AND GUT MICROBES

GABA, the chief inhibitory neurotransmitter in the brain, regulates various physiological and psychological processes and its dysfunction can lead to several neuropsychiatric disorders like depression [37]. GABA is widely distributed in the human brain, with concentrations ranging from 1-2 mM/kg of tissue and present in 10-40% of the nerve terminals in the cerebral cortex, substantia nigra, and hippocampus. The synaptic effects of GABA in the central nervous system are mediated through two major receptor subtypes, termed GABA_A and GABA_B. Depression is associated with lower levels of GABA in cerebrospinal fluid [38].

GABA level was reported to be reduced in the dorsolateral prefrontal and occipital cortex of depressed patients based on various neuroimaging analyses [39-43]. GABA-producing

pathways are actively expressed by *Bacteroides*, *Parabacteroides*, and *Escherichia species*, according to a transcriptome analysis of human stool samples from healthy people. By coupling 16S ribosomal RNA sequencing with functional magnetic resonance imaging in patients with major depressive disorder, the researchers found out that the relative abundance levels of faecal *Bacteroides* are negatively correlated with brain signatures associated with depression [44]. According to newer evidence, the Glutamate decarboxylase (GAD) -encoding gene (major enzyme producing GABA) is prominent in the human intestinal genus *Bacteroides*. The GAD-system consists of at least four highly conserved genes encoding a GAD, a glutaminase, a glutamate/GABA antiporter, and a potassium channel with the high prevalence of the GAD-system among *Bacteroides*. Studies had shown glutamate and glutamine as precursors of GABA production and *Bacteroides* have an important role in the regulation of the GABAergic system in the human gut [45]. Alteration in bacterially derived GABA and/or GAD-system genes may account for mental health issues like depression [44,46].

GUT MICROBIOTA COMPOSITION ALTERATION IN DEPRESSION

The richness of specific microorganisms in depressive patients appears to be altered in various studies conducted by the researchers across the globe. The Flemish researchers investigated the gut microbiota of 1,054 participants, living in the Belgium province of Flanders in the study Flemish Gut Flora Project. They discovered that the gut microbiota of persons who had been diagnosed with depression was consistently depleted in two genera of bacteria (*Coprococcus* and *Dialister*) [47].

A study conducted by Jiang et al, states that the abundances of *Lactobacillus* and *Bifidobacterium* were decreased in depressed subjects and in line with these findings, they also reported an under representation of *Firmicutes* but an over representation of *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* in fecal samples from depressed patients [48]. Although the sample size is small in a study conducted by Naseribafrouei, et al., found out that there is a higher proportion of *Bacteroidales* and significantly lower levels of *Lachnospiraceae* associated with depression [49]. A study conducted by Meng Yu et al in a rat model of chronic variable stress (CVS)-induced depression exhibits decreased relative abundances of the bacterial genera *Corynebacterium*, *Psychrobacter*, *Lactobacillus*, *Peptostreptococcaceae incertae sedis*, *Clostridiales*, and *Coprococcus* [50]. In a study using chronic restraint stress (CRS) model of depression, the depressed mice compared against control group and found out the changes in bacterial taxa between groups like decreased abundance of genus *Akkermansia* in depressed mice [29]. A study conducted in irritable bowel syndrome (IBS) patients had shown a negative correlation with abundance of *Lachnospiraceae* and depression [51].

TENTPOLES FOR MAINTAINING A HEALTHY GUT MICROBIOME

1) DIET

A well-balanced diet enriched with essential nutrients can help to build a healthy gut microbiome. A healthy gut may show richness of specific species. The addition or deletion of species has an impact on microbiome function. People's dietary choices influence their gut microorganisms by providing substrates for some species and providing a competitive advantage over other GI microbiota. The more diverse the diet, the more diverse the microbiome and the more adaptive it will be to environmental changes [52]. The gut microbiota of rural people is different from the urban people be-

cause of their dietary patterns enriched with high fibers [53-57]. With the advent of western lifestyle and urbanization, the food habit got changed and posed a threat to the extinction of fiber-degrading bacteria [58]. It is important to include vegetables and fruits in your diet since it is digested by certain bacteria in your gut, which stimulates their growth, which have a positive influence on mental health and protect against depressive symptoms [59,60]. Fermented food can also improve gut microbes like *Lactobacillus* and *Bifidobacteria* species and thereby improve brain health via direct and indirect pathways [61]. Some examples of fermented foods are yogurt, kimchi, sauerkraut, kefir, kombucha, tempeh etc [59]. Polyphenols are natural compounds found in a wide variety of foods and are particularly high in plant-based foods exert protective effects on mental health and help in reducing depression risk across several populations. Food items rich in polyphenols are cocoa, dark chocolate, red wine, grape skins, green tea, almonds, onions, blueberries, broccoli etc. [62,59].

2) PROBIOTICS AND PREBIOTICS

Probiotics are live microbes (usually lactic acid bacteria such as *Lactobacilli* and *Bifidobacteria*) that benefit the host by promoting intestinal ecosystem balance. Probiotics are marketed in the form of capsules, powder, or fermented products [63]. The possible mechanistic role of probiotics in depression through their anti-inflammatory effects, restoration of gut permeability, modulation of neurotransmitters, attenuation of HPA axis and epigenetic mechanism. The administration of probiotics has also been shown to restore and elevate the depleted levels of the neurotransmitters of interest, namely, 5-HT, DA, NE, and GABA, which have been observed in depression. *Lactobacilli reuteri*, *Bifidobacterium infantis* and *Bifidobacterium adolescentis* are examples of probiotics which exert anti-inflammatory effects that could improve depressive symptoms [64]. Probiotics are generally safe for consumption, except for immune-compromised and critically sick individuals wherein probiotics may cause sepsis, pneumonia, endocarditis, and allergies [65]. Prebiotics are nondigestible compounds that, through its metabolism by microorganisms in the gut, modulates the composition and/or activity of the gut microbiota, thus conferring a beneficial physiologic effect on the host [66]. These are known to stimulate enteric microbial growth that have been associated with positive effects on mood and emotions [67]. Health benefits of prebiotic dietary fibers includes increases *bifidobacteria* and *lactobacilli* and decreases pathogenic bacteria populations [68]. Probiotics alone or combined with prebiotics may help in reduction of depression [69]. Although some studies states that probiotic doesn't have a significant effect on reduction in depression [67,70].

3) SLEEP

Sleep deprivation may alter microbial community structures. The circadian rhythm of intestinal microbes shows significant diurnal fluctuations that result in time-of-day-specific taxonomic configurations related to dietary structure, circadian rhythm, and gender of the host. Depression and sleep are both closely related to circadian activity. The disruption of the host circadian rhythm shatters the clock of gut microbiome and thereby alteration in gut microbiome equilibrium [71]. Short-term partial sleep deprivation may also have minor impacts on the human microbiome [72].

4) EXERCISE

Emerging body of science suggests that the beneficial impact of exercise on gut microbiota diversity. A study conducted among 40 professional rugby players showed that

the athletes' microbiomes were far more diverse than those of two control groups of normal people^[73]. A study conducted among rats also showed a significant increase in the number of *Lactobacillus*, *Bifidobacterium*, *Blautia coccoides*, *Eubacterium rectale* in the rats undergone physical activity^[74]. Microbial profiles of physically fit individuals had an increased microbiota diversity, increased abundances of key butyrate-producing taxa of *Clostridiales*, *Roseburia*, *Lachnospiraceae*, and *Erysipelotrichaceae*, which is likely contributed to an increase in butyrate levels^[75].

5) ANTIBIOTICS

Gastro intestinal microbiome when exposed to the antibiotics, produce substantial taxonomic and functional changes. Agricultural practices of using antibiotics as growth promoters for poultry, swine and cattle further narrow the GI microbiome^[52]. Mice treated with Ampicillin, Streptomycin, and Clindamycin showed a dramatic decrease in abundance of beneficial bacteria including *Bifidobacterium* and *Lactobacillus*^[76]. Several studies demonstrated that the specific antibiotic or antibiotic cocktail can lead to depressive behavior. Amoxicillin administration in juvenile rats caused a significant increase in the immobility time and reduction of swimming time of these animals indicating depression-like behavior^[77]. Mice treated with ciprofloxacin had depressive behavior when compared with the controls^[78]. Rat treated with antibiotic cocktail (ampicillin, vancomycin and ciprofloxacin, imipenem, and metronidazole) displayed great depressive-like behaviors as indicated by a decreased swimming and increased immobility scores^[79]. In a large population-based medical record database study from the United Kingdom showed recurrent antibiotic exposure is associated with increased risk for depression and anxiety^[80].

6) STRESS

Stress can affect health through its impact on gut bacteria. Acute and chronic stress can induce a significant alteration in gut microbes of rodents^[81-83]. Repeated exposure to social stress can alter the diversity and composition of gut microbiota, accompanied by changes in microbial metabolites, cytokines, chemokines, and monoamine transmitters, which regulate behavior by stimulating the peripheral and central nervous systems^[84,85]. In a psychological-stress model study, rat undergone stress had induced changes in gut microbiota with increased intestinal barrier and BBB permeability in the bidirectional interaction between gut microbiota and psychological stress^[86]. Chronic stress causes dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to an increased level of glucocorticoids that contribute to the development of neuropsychiatric disorders such as anxiety and depression^[87,88].

CONCLUSION

Most of the treatment strategies for depression focus on neurotransmitter levels or external factors like social stress but newly evolving studies in relation to gut microbes and depression may help these less discussed areas to sound profoundly and thus provide a helping hand to develop novel strategies for depression management. The limited number of research in this field made the explanation of the gut microbes and mental health bit more challenging. More research is needed to determine the effects of probiotic/prebiotic use, a healthy diet, adequate sleep, antibiotic use, and stress reduction in promoting stable brain processing.

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