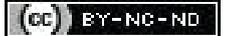


Microbiota-gut-brain Axis and its Role in Depression: A Narrative Review

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ABSTRACT

The mutual peaceful coexistence of microbiota with their host ensures normal gut motility and secretory functions, mucosal immune function and absorption of nutrients. Emerging evidences suggest the role of gut microbiota in a bidirectional communication between Central Nervous System (CNS) and gastrointestinal system, referred to as gut-brain axis. The findings largely drawn from preclinical studies show that gut microbiome can modulate brain and behaviour via vagal nerve, inducing tryptophan metabolism pathways, affecting synthesis of neurotransmitters, production of bacterial metabolites, such as Short-Chain Fatty Acids (SCFAs), by Hypothalamus-Pituitary-Adrenal Axis (HPA) alterations and through neuroimmune pathways. Psychological stress could lead to abnormal changes in composition of gut microbiome and disruption of intestinal barrier functions and it also has an underlying role in neurobiology of depression which has multifactorial aetiology. The perturbations of gut microbiota have been associated with depression and might have a contributory role in development of depressive symptomatology. The current understanding of microbiota gut-brain axis is still in early stages and drawn from preclinical and clinical data and therefore it warrants further research to elucidate its role in stress and depression and future development of novel therapies targeting microbiota-gut-brain axis for stress related disorders such as depression.

Keywords: Depressive disorder, Dysbiosis, Gastrointestinal disorders, Microbiome, Probiotics, Psychological stress

INTRODUCTION

Recent and growing evidence has shown tremendous progress in evaluating the role of gut microbiota, acting as a link in signaling between gastrointestinal system and CNS, which is referred as gut-brain axis communication [1]. The peaceful mutualistic coexistence of gut microbiota with host is crucial for key processes such as development of intestinal mucosal and systemic immune system and acting as a physical barrier to incoming pathogens. The other pivotal roles conferred by gut microbiota to host health are modulating gut motility, absorption of nutrients and fat distribution [2]. Accumulating evidence suggests the role of gut microbiota in regulating stress, cognition and behaviour have been largely drawn from experimental findings in animal studies [3]. Disruption of the symbiotic relationship between intestinal host and microbiota which is known as dysbiosis may result in perturbations of host functions and confer disease susceptibility [4]. Recent research has implicated the role of altered gut-brain axis in gastrointestinal disorders such as Irritable Bowel Syndrome (IBS) as they have been found to be highly co-morbid with stress related disorders such as depression [5,6]. Thus, recent interest has grown towards gut-brain axis, as a target for development of novel therapies by modulating gut-brain axis for several stress related disorders including anxiety, depression and functional gastrointestinal disorders [7]. In the current review we will discuss the role of gut microbiota in gut-brain interactions, the role of gut microbiota-gut-brain-axis in stress and depression, the possible role Faecal Microbiota Transplantation (FMT) and probiotics could play as a novel therapeutic target for stress related disorders such as depression in future.

Gut Microbiota Diversity

The human gastrointestinal tract harbours 10^{14} micro-organisms, which are ten times the number of human cells in the body and the collective genome of all of the microorganisms in a microbiota referred as microbiome is 150 times larger than host's genome [8]. The microbiota is the collection of microorganisms living in a particular habitat, besides gut ecosystem which is densely colonised, these organisms inhabit the body surfaces of such as skin, genitourinary

system and respiratory tracts [8,9]. The composition of gut microbiota is dominated by the strict anaerobes, compared to facultative anaerobes and aerobes [9]. The microbiome contains approximately 500-1000 species and more than 7000 strains, which although harbours viruses, protozoa, fungi and archae but largely dominated by strict anaerobes particularly of Bacteroidetes and Firmicutes phyla, while Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia phyla are in relatively lesser abundance [10]. Perturbations of any kind such as antibiotic exposure, infections of gastrointestinal system may affect the stable habitat resulting in alteration in its microbial composition [4].

Microbiota-gut-brain Axis: A Bidirectional Link

The gut-brain axis is a bidirectional communication between microbiota within the gut and CNS, mediated by neural, endocrine and immune mechanisms from gut microbiota to brain and brain to gut microbiota. The gut-brain axis communication comprises of CNS, neuroendocrine, neuroimmune, parasympathetic and sympathetic branches of autonomic nervous system, the Enteric Nervous System (ENS) and intestinal microbiota [11]. The afferent signals initiating from the gut through means of several direct and indirect pathways projects to CNS structures, converse visceral messages from gut thereby influencing brain function. Whereas, efferent signals from brain converge to intestinal smooth muscles in gut, thereby influencing gut motility and secretory functions [12]. However, the multiple direct and indirect pathways involved in bidirectional communication between gut and brain are yet to be conclusively established, some potential mechanisms have been proposed to be involved in signalling [13]. They include neural pathways which comprises of vagus nerve and ENS. The other route of communication is through immune pathways which consist of cytokines produced by mucosal immune cells, neuroendocrine pathways that is Hypothalamic Pituitary Adrenal (HPA) axis and cortisol, in addition to these, the tryptophan metabolism, production of Short Chain Fatty Acids (SCFAs) and neurotransmitters also appears to play a role in these interactions [13].

Tryptophan is a precursor of serotonin which plays a major role in mood and cognition and is a key neurotransmitter of brain gut

axis. Majority of serotonin synthesis takes place in the periphery enterochromaffin cells in gut, being the largest source [14]. Kynurenine pathway accounts for the most of the peripheral tryptophan metabolism. Kynurenine is synthesised by the activity of indoleamine 2,3 dioxigenase or hepatic based enzyme tryptophan 2,3 dioxigenase and their activity can be induced by inflammatory cytokines and by glucocorticoids [12].

There is also growing evidence that gut microbiota has the ability to generate neurotransmitters and neuromodulators and further these may modulate neural signaling within ENS [15]. *Candida*, *Escherichia*, *Streptococcus* and *Enterococcus* species synthesise 5-hydroxytryptamine (5-HT), *Bacillus* generates dopamine, certain *Lactobacillus* and *Bifidobacterium* species produce Gamma-Aminobutyric Acid (GABA), *Lactobacillus* produces acetylcholine, while *Escherichia*, *Bacillus* and *Saccharomyces* species synthesise norepinephrine (NE) [16].

Neuroactive bacterial metabolite such as SCFAs includes n-butyrate, acetate and propionate, are derived from digestion of dietary fiber (complex carbohydrates) and subsequent fermentation by gut microbes can also signal the brain [15]. Research using Germ Free (GF) animals have helped to provide a novel insight regarding the role of gut microbiota in gut brain signaling in addition to its contribution to host's health and disease. The GF animal term is used to refer to animal which is raised without any exposure to microorganisms [17]. While Specific Pathogen Free (SPF) animals are those that exclude particular pathogens [17].

Gut Microbiota in Stress and Depression

The HPA axis is a neuroendocrine system which plays a pivotal role in regulation of adaptive responses to stress. Environmental factors such as stress or proinflammatory cytokines can activate HPA axis resulting in secretion of Corticotropin Releasing Factor (CRF) from hypothalamus, which further induces the release of Adrenocorticotrophic Hormone (ACTH) secretion from anterior pituitary, further ACTH stimulates the synthesis and secretion of glucocorticoids from adrenal cortex, cortisol in humans and corticosterone in animals [18].

Researches have long suggested the ability of psychological stress such as maternal separation, restraint conditions and the exaggerated HPA axis activity to alter the composition of gut microbiota [18,19]. Several preclinical studies in GF animals or SPF animals along with experimental models by inducing perturbations of microbiota composition such as antibiotic administration and deliberate infections and interventions by administering probiotics have played a pivotal role in ascertaining the effect of psychological stress on composition of commensal microbes as well as the commensals role in stress and behaviour [20,21]. Bailey MT et al., observed that offsprings of rhesus monkey exposed to prenatal stressors in early gestation exhibited *Lactobacilli* depletion, whereas infants from late stress pregnancies showed reduction of both *Bifidobacteria* and *lactobacilli* [22]. Moreover, stress exposed infants also showed a tendency for subclinical colonisation by pathogen *shigella flexneri* [22]. Likewise infant rhesus monkeys maternally separated exhibited decrease in faecal *lactobacilli* on day 3 post separation, then coming to baseline by end of week [23]. In separated infants decrease in microflora correlated with display of stress indicative behaviour and showed increased susceptibility to opportunistic bacterial infection. However, decreased *lactobacilli* levels were not correlated with elevated cortisol secretion in separated offsprings [23].

In another study on exposure to prolonged restraint stressor the adult stressed mice showed reduction in microbial richness and diversity and led to an increased in susceptibility to *Citrobacter rodentium* an enteric pathogen compared to non-stressed control mice [24]. In a study by O'mahony SM et al., rat pups during early life were maternally separated for three hours daily, between postnatal day 2-12 showed increased levels of corticosterone and

increased systemic immune response in form of increased levels of inflammatory cytokines relative to non-separated controls [25]. In addition, maternal separation also resulted in alteration of faecal microbiota communities [25], these results could provide an insight into the plausible role of altered gut-brain axis in stress related disorders such as depression [21]. In another study maternally separated mice showed increased peripheral release of Interleukin-6 (IL-6) and increased amygdala CRF mRNA levels and following a *Bifidobacterium infantis* treatment resulted in normalisation of the immune response [26].

Psychological stress in a form of maternal separation has shown to increased intestinal permeability by disrupting intestinal barrier which could lead to microbiota driven mucosal inflammation further causing an alteration in proinflammatory cytokines and subsequent activation of HPA axis [27]. Furthermore, it has been suggested that increased translocation of Lipopolysaccharide (LPS) of gram-negative bacteria (leaky gut) enterobacteria along with increased gastrointestinal permeability might contribute to inflammatory pathophysiology of depression as some studies have found increased bacterial translocation in patients of depression particularly in chronic depression [28]. As depression is a neuropsychiatric disorder with a multifactorial aetiology in which psychological stress and low-grade inflammation, in subset of patients could also contribute to the neurobiology of depression, therefore gut microbiota might provide a possible link between them [29].

Gut Microbiota Composition and Diversity in Depression

Alpha diversity explores the number of taxa (richness), distribution, evenness (the relative abundance of those taxa) of bacterial species within the host, while beta diversity focuses in gut microbiota ecology between individual groups, such as between depressive patients and healthy controls [30]. In depressive patients several studies, including systematic reviews and meta-analysis have been done to investigate the faecal microbiota composition and diversity in depressive patients, when compared to healthy controls [29,31]. Jiang H et al., observed changes in the faecal microbiota composition in major depressive patients and a negative correlation was observed between *Faecalibacterium* and the severity of depressive symptoms [32].

In addition, Radjabzadeh D et al., investigated the relation of faecal microbiome diversity and composition with depressive symptoms and identified association of thirteen microbial taxa with depressive symptoms, known to be involved in the synthesis of glutamate, butyrate, serotonin and GABA, which are key neurotransmitters for depression [33].

However, McGuinness AJ et al., found no strong evidence for a difference in the number or distribution of gut bacteria (alpha-diversity) in those with a mental disorder including Major Depressive Disorder (MDD) compared to controls [34]. Previous clinical studies have shown inconsistent findings while analysing the association between gut microbiome and depression, it may have been contributed by numerous factors such as dietary habit, use of psychotropic medication, age, gender and Body Mass Index (BMI) in depressive patients [34-37]. Gao M et al., in a systematic review and meta-analysis, found no difference in alpha diversity indices, Firmicutes and Bacteroidetes levels in depressive patients compared with healthy controls [37]. Additionally, in a subgroup meta-analysis, Firmicutes level was decreased in medication-free depressive patients but Bacteroidetes level was elevated [37]. Moreover, the higher abundance of proinflammatory genera (*Enterococcus*, *Eggerthella*) and depletion of certain anti-inflammatory butyrate-producing bacteria (i.e., *Butyrivibrio*, *Coprococcus*, *Faecalibacterium*, *Fusicatenibacter*, *Eubacterium ventriosum* group, *Romboutsia*), was observed in psychiatric disorders including depression, relative to controls in a meta-analysis study [38].

Faecal Microbiota Transplantation (FMT) studies in depression

Preclinical Studies: The data from preclinical studies have indicated the effect of FMT from depression patients to GF mice resulting in a depression like behaviours in recipient mice, thereby suggesting that depression-associated alterations in the gut microbiome specifically influences aspects of depression like behaviour and physiology via a gut microbiota transfer [39,40].

Zheng P et al., observed when gut microbiota of depressive patients was transplanted to GF mice, it resulted in depression like behaviour, compared with 'healthy gut microbiota' transfer from healthy controls [41]. Moreover, gut microbiota composition of depressive patient and healthy controls were different, with changes in relative abundance of Firmicutes, Actinobacteria and Bacteroidetes [41]. Kelly JR et al., also demonstrated that depression was associated with decreased gut microbiota richness and diversity [42]. Furthermore, transfer of gut microbiota from healthy individuals to depression animal model showed amelioration of depressive symptoms. Many preclinical investigations reported following FMT treatment, there was reversal of Chronic Unpredictable Mild Stress (CUMS) induced depression symptoms in depression animal models, increased hippocampal Brain-Derived Neurotrophic Factor (BDNF), 5-hydroxytryptamine (5-HT), GABA levels, while hippocampal glutamate (Glu) level, systemic inflammatory mediators (LPS, interleukin IL-6, interleukin IL-1 β , Tumour necrosis factor TNF- α) and inflammasomes in rats brain such as caspase-1, Interleukin-1 β (IL-1 β) were decreased [43-47]. FMT improved the gut microbiota imbalance, alleviated intestinal tract inflammation and neuroinflammation in some CUMS animal models [46,47]. Inflammation has been shown to play a key role in neurobiology of depression [48]. Previous research has exhibited high level of pro-inflammatory cytokines, and low levels of anti-inflammatory cytokines in a subset of patients with depression [48]. Moreover, depression animals treated with FMT, showed enhancement of lactobacillaceae, Prevotellaceae, Firmicutes, while the levels of Dialisters sp., Desulfobacterota, Bacteroidetes, Desulfovibrionaceae, γ Proteobacteria were reduced [44-46]. All of the above-mentioned animal studies reflects the potential role of gut microbiota signaling in modulating stress induced depression like behaviour [39].

Clinical Studies: The FMT from healthy individuals improved depressive symptoms in patients by restoring gut microbial balance, albeit temporarily [29,49]. Likewise, several clinical trials have assessed the FMT from healthy individuals to depressive IBS patients and found short term improvement in depression symptoms however, long term effects were inconsistent [50-53]. Mizuno S et al., reported that FMT significantly improved the psychological status, which was assessed by Hamilton Depression Rating Scale (HAM-D) score at 4 weeks after FMT, but returned to the baseline level at 12 weeks in IBS patients [51]. Moreover, there was significant increase in microbial diversity from before treatment to 4 weeks after FMT in patients [51]. Similarly, Huang HL et al., observed improved HAMD scores at one month and three months after FMT from healthy individuals in IBS patients, which was sustained till six months after the first procedure [52]. Mazzawi T et al., reported significant improvement in Hospital Anxiety and Depression (HAD), depression scores three weeks after FMT and improvement lasted up to 20 weeks in IBS subjects [53].

Furthermore, in a case report, two patients with MDD in a Randomised Controlled Trial (RCT) treated with FMT as an add-on therapy. Both MDD patients improved their depressive symptoms four weeks after the transplantation compared to baseline scores (In patient 1 and 2, HAMD-scores decreased from 21 to 9 points and from 31 to 10 points, respectively) [54]. Additionally, the effects lasted up to eight weeks in one patient [54]. However, in another case report study showed improved depressive symptoms during the 18-month follow-up after six rounds of FMT. Similarly, Kurokawa S et al., also confirmed significant improvement in HAM-D scores

and microbiota diversity following FMT procedure. Interventions targeting the gut-brain axis with FMT through restoration of gut microbiome via faecal transplant from a healthy donor, suggests the potential of FMT in therapeutic option as an adjunctive to existing treatments in future, which may be helpful in alleviating depressive symptoms as shown in preclinical and clinical investigations [55]. However, it warrants further studies with larger sample sizes to establish its efficacy and safety [39].

Probiotics in Depression

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host [56]. Several preclinical and clinical studies have investigated the beneficial effect of probiotic supplementation on depressive symptoms [57-60]. Abildgaard A et al., concluded probiotic treatment independent of diet, resulted in significant decrease in depressive-like behaviours in rats [57]. Similarly, in another study a combination of *Lactobacillus helveticus* and *Bifidobacterium longum* alleviated depression like behaviours, evident post myocardial infarction in rats, which appeared to be mediated by restoring intestinal permeability by probiotics [58].

Probiotics by virtue of restoring the composition and diversity of gut microbiota, modulating inflammation and restoring gut barrier integrity may provide a novel way to treat depressive patients as an adjunctive therapy [61]. The findings by Lin H et al., have substantiated the therapeutic potential of probiotics in mitigating depressive symptoms by reducing depression scores [62]. A meta-analysis conducted in depression patients without major comorbidities, concluded in a subgroup analysis, that probiotics improved depressive symptoms in patients with both mild and moderate depression compared to placebo [63]. A systematic review and a meta-analysis investigated the effects of probiotics on depression and found that probiotics were associated with a significant reduction in depression symptoms [64]. Additionally in a meta-analysis of 19 double-blind, randomised, placebo-controlled trials with a total of 1901 participants by Goh KK et al., found probiotics were effective in reducing depressive symptoms in those with major depression, but not in those with other clinical conditions and in healthy individuals [65].

In another meta-analysis by Ng QX et al., showed no improvement of mood in the treatment group when compared to placebo group post-intervention, however in a subgroup analysis demonstrated significant improvements in the moods of individuals with mild to moderate depressive symptoms but not in healthy individuals [66]. The studies have shown the efficacy of probiotics such as *Bifidobacterium* (e.g., *B. longum*, *B. breve*, and *B. infantis*) and *Lactobacillus* (e.g., *L. helveticus*, *L. rhamnosus*, *L. casei*), in improving mood symptoms [29,67].

Schaub AC et al., documented amelioration of depressive symptoms (reflected by decreased HAM-D scores) relative to placebo group, after a short-term high dose probiotic supplementation as an add-on treatment for depression [68]. In addition, Probiotics maintained microbial diversity and increased abundance of the genus *Lactobacillus* in probiotics group was associated with decreased depressive symptoms [67]. Similarly, Nikolova VL et al., observed probiotics were effective in amelioration of depressive symptoms in clinically depressive patients when given in addition to antidepressants as an adjunctive therapy, however were not effective when used as stand-alone treatment [69]. Additionally, In a double-blind, placebo-controlled pilot randomised clinical trial, 8-week adjunctive treatment with a multistrain probiotic was found to be acceptable and tolerable for participants with MDD, although the depressive symptoms improved in both the groups (Hamilton Depression Rating Scale (HAM-D-17) and Inventory of Depressive Symptomatology (IDS) scores), but greater reductions in depressive scores were seen in the probiotic group from week four compared

to placebo (Participants were evaluated at baseline, week 4, and week 8) [70].

Gut microbiota has the ability to influence the interactions between gut and brain and alteration of gut-brain axis has been suggested to play a role in several neuropsychiatric disorders such as depression [30]. The findings suggesting the ability of certain probiotics strains to modulate depression symptoms appears promising and may provide a novel therapeutic target to be used therapeutically as an adjunctive therapy for depression in future [61]. Although the data from the existing preclinical and clinical studies are compelling and findings are promising pertaining to beneficial effects of interventions such as probiotics and FMT in depressive symptoms, further research warrants, with appropriately designed controlled trials with larger sample size [39]. The focus of future studies should also be about to elucidate the strain-specific effects of probiotics, dosage, treatment durations, and particularly safety and efficacy of these interventions [39,71].

CONCLUSION(S)

The gut microbiota balance is pivotal for human health. In recent researches, depression has been found to be associated with gut dysbiosis that is alteration in microbial composition and diversity when compared to healthy individuals. The gut microbiota being capable of modulation by certain factors for instance, supplementation with live microorganisms thus has emerged as a promising novel therapeutic target for depression in future.

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PLAGIARISM CHECKING METHODS: [\[Jain H et al.\]](#)

- Plagiarism X-checker: May 07, 2025
- Manual Googling: Aug 30, 2025
- iThenticate Software: Sep 01, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 25, 2025**
Date of Peer Review: **Aug 06, 2025**
Date of Acceptance: **Sep 03, 2025**
Date of Publishing: **Apr 01, 2026**