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Research Article

Role of Gut Microbes in Different Psychiatric Disorders

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Abstract

Background: As mental disorders are on the rise all over the world, it has become crucial to understand the pathophysiology of the various disorders so as to come up with effective treatment options. However, in the process of understanding the pathophysiology of psychiatric disorders an important aspect of it - the microscopic organisms of our body, i.e., gut microbes are ignored. Gut microbes are crucial not only in digestive health but also in mental health. Thus, it is important to bring the role gut microbes into the limelight and understand how alterations in the good gut microbes can lead to disruptions in the body resulting in disorders of every organ. Understanding the role of gut microbes in brain activities and brain health can lead to a new treatment approach in the psychiatric world as traditional psychiatric medications carry a lot of side effects. The aim of this current review is to introduce the brain-gut-microbiota axis, to briefly describe evidence from studies and lastly to discuss the cause-effect relationship between the gut microbiome and mood disorders.

Objective: Studying the role of gut microbes in different psychiatric disorders.

Methodology: We have taken into account the recent clinical studies to establish the relationship between gut microbes and psychiatric disorders. We have opted stress, anxiety, depression, autism and mood disorder to cover most common psychiatric disorders and their association with gut microbes. We have put a clear analysis of the studies done on effect of probiotics on psychiatric disorders to establish the understanding how alterations in gut microbes can open a new door for treatment trials.

Result: Probiotics in autism has shown a great result in the clinical trials which itself establishes the role of gut microbes in the disorder. There is again a clear relationship establishment of gut microbes and stress as the gut microbes play vital role in neuroendocrine axis and hormones and neurotransmitters formation, it is evident that gut microbes are directly involved in stress along with the dietary habits and residing environment of the person. Reduction in number of gut microbes can manifest as stress, anxiety and other psychiatric disorders as they play an important role in gut-brain axis. Balanced and healthy number of gut microbes help in reducing the inflammation in the brain hence reducing the stress load of the brain and enhancing its functioning.

Keywords: *Gut Microbes; Psychiatric Disorders; Gut Brain Axis*

Abbreviations

SZ: Schizophrenia; BD: Bipolar Disorder; MDD: Major Depressive Disorder; ASD: Autism Spectrum Disorder; AD: Anxiety Disorders; GI: Gastrointestinal; MSG: Monosodium Glutamate; 5-HT: Serotonin; HPA: Hypothalamic-Pituitary-Adrenal Axis; GF: Germ Free Mice; SPF:

Specific Pathogen Free Mice; CNS: Central Nervous System; ACTH: Adrenocorticotropic Hormone; EEC: Enteroendocrine Cells; GABA: Gamma-Aminobutyric Acid; TLRs: Toll-Like Receptors; PRR: Pattern Recognition Receptor; PAMPs: Pathogen-Associated Molecular Patterns; SCFAs: Short Chain Fatty Acids; TMA: Trimethylamines; TMAO: Trimethylamine-N-Oxide; FMOs: Flavin-Containing Monooxygenases; BBB: Blood Brain Barrier

Introduction

Psychiatry world had been shown many challenges during its discovery mainly due to its absent and unclear etiology and pathophysiology. Regarding that, it is important to notice the relation of psychiatric disorders and many medical chapters in order to have the accurate etiology with the physiological mechanism known in order help psychiatric patients with diagnosis and treatment reduce and eliminate their suffering.

New psychiatric disorders are being discovered everyday making it important to further our understanding of the various aspects of these disorders. Research on psychiatric disorders such as schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), autism spectrum disorder (ASD) and anxiety disorders (AD) has been going on for years. Many studies have contributed towards understanding the neuroendocrine, neuroimmune and genetic mechanisms of these disorders. However, the etiology and mechanisms of pathophysiology have been neglected until recently. Scientists are taking a new approach to better understand these disorders. The role of gut microbiota is one facet of this new approach that may provide clarity on the etiology or even the pathophysiology of the various psychiatric disorders.

Gut microbiota are symbiotic bacteria which live in our gastrointestinal (GI) system organs, the majority in colon and rest between stomach and ileum. Gut microbiota is functioning in metabolic machinery way. Beside this function, it is known its influence on hormones regulation, immunological way and in neuroscience as well. Regarding of noticing the gut microbiota effect on neuroscience, its relation with central nervous system had been named as "microbiota-gut-brain axis".

Contributing to many studies were involved in the discovery of the relation between gut microbiota and neuropsychiatry world, studies had been done to differentiate between gut microbiota composition in mental disorders people in compared controls. Additional to that, studies had studies this relation in understanding psychiatric disorders symptom's severity as well. Studies had shown impact of gut microbiota in psychiatric disorders. *Faecalibacterium* were effective in bipolar disorder and major depressive disorder. Schizophrenia SZ had been affected regarding studies from *Firmicutes, Haemophilus* and *Lachnoclostridium*. Severity of psychiatric disorders had been noticed with *Bifidobacterium, Coprococcus* and *Ruminococcaceae*.

The turn of understanding of gut microbiota was significantly important in understanding the etiological relation of psychiatric disorders with gut microbiota. Gut microbiota had been affected regarding many reasons according to clinical studies. Life style behaviour have great impact on gut microbiota changes mechanism and counting, smoking, physical activity and sleep had shown main effect in gut microbiota. Additional to that, it was found the effect of yogurt and milk in gut microbe was noticed in improving the pathophysiological mechanism in gut microbiota. This information was mainly regarding studies that had confirmed the effect of use probiotics, antibiotics, prebiotics and synbiotics with gut microbiota [42].

Gut microbiota physiology

The gut microbiota also known as the gut microbiome refers to the vast array of microorganisms found colonizing a majority of our colon, along with a small part of our stomach and ileum. At present, the gut microbiome is estimated to exceed 10^{14} microbial cells, a number that is ten times greater than that of human cells found in the body [21]. It mainly comprises bacteria, followed by viruses, fungi, protozoa and archaea [21,22]. It is worth noting that the composition of the microbiome is specific to individuals and heavily relies on genetics, growth, and development. Although commonly referred to as the commensal bacteria, the microbiome-human host relationship is better described as one being based on mutualism rather than commensalism [23]. This is primarily because following the establishment of the

microbiome at birth, it is involved in several physiologically significant functions. Our body in turn provides them with the nutrients and anaerobic environment required for their sustenance.

Ensuing multiple studies conducted on germ-free mice and humans alike, it can be said that the gut microbiome influences and shares a relationship with the brain, immune system, and metabolic and structural functions.

Microbiota and immune response

Although the intestinal mucosa provides the first line of defense, some bacteria can get through this barrier and cause an inflammatory response. The intestinal mucosa, therefore, relies on the ability of the innate immunity to differentiate between microbiota and potential pathogens to maintain healthy physiological functioning and homeostasis. This characteristic ability of innate immunity is due to the presence of toll-like receptors (TLRs), a type of pattern recognition receptor (PRR) found in intestinal dendritic cells. These cells recognize specific pathogen-associated molecular patterns (PAMPs), following which they activate transcription factors that stimulate the expression of genes encoding cytokines and other anti-microbial molecules [24]. The most important transcription factors activated are those of the nuclear factor κB (NF-κB) family, which promote the expression of various cytokines and endothelial adhesion molecules, and interferon regulatory factors (IRFs), which stimulate the production of the antiviral cytokines, type I interferons [25]. In addition, TLRs also stimulate the activation of regulatory T-lymphocytes, which suppresses the inflammatory response to microbiota, while simultaneously stimulating the helper and cytotoxic T-lymphocytes to work against potential pathogens.

Furthermore, the TLRs also have a direct role in boosting the integrity of the intestinal epithelium through the translocation of zonula-occludens 1, a tight junction protein [21].

The gut microbiota is also essential in developing gut-associated lymphoid tissue (GALT), a critical component of GI immunity [21].

Microbiota and their by-products

Microbial-derived metabolites and dietary components (short-chain fatty acids, trimethylamines, amino acid derivatives, and vitamins) have essential metabolic and signaling functions which can modulate host homeostasis, including BBB integrity and brain function.

Short chain fatty acids (SCFAs)

The microbiota-induced digestion and fermentation of dietary metabolism give rise to short chain fatty acids - acetate, propionate, and butyrate, which then modulate energy release and aid microbial growth. SCFAs can stimulate colonic blood flow, and upper gut motility, improve satiety and enhance salt and water uptake. Intravenous administration of sodium butyrate, following traumatic brain injury, has been shown to reduce BBB breakdown and promote neurogenesis. Additionally, the intraperitoneal injection of butyrate in germ-free aging mice has been shown to improve neuroinflammation. When administered intracerebroventricularly in CK - p25 transgenic mice, exhibiting the hallmark synaptic and neuronal loss seen in Alzheimer's disease, butyrate has been found to enhance memory and learning. Protective, anti-inflammatory effects have also been seen with propionate in a human brain endothelial cell culture. The SCFAs also regulate the synthesis and release of gut-derived 5-HT from enteroendocrine cells [23].

Trimethylamines

Trimethylamines (TMA) are the by-products of microbial choline metabolism. In the liver, TMA is converted to trimethylamine-N-oxide (TMAO) in a reaction catalyzed by flavin-containing monooxygenases (FMOs). Gut-derived TMA is generated by bacteria of the genera *Anaerococcus, Clostridium, Escherichia, Proteus, Providencia,* and *Edwardsiella*. The beneficial effects of TMA include decreased endoplasmic reticulum stress and lipogenesis in adipocytes, increased insulin secretion, and diminished diet-induced impaired glucose tolerance. Besides these effects, TMAO has also been found to restore the ability of mutant tau protein to promote microtubule assembly with microtubule disassembly and neuron death being some of the hallmark features of Alzheimer's disease. Coming to its detrimental effects, TMAO is associated with an increased risk of colorectal cancer, atherosclerosis, and cardiovascular disease through its effects on cholesterol metabolism. This provides a direct contrast to its therapeutic effects in Alzheimer's disease since cardiovascular disease

and altered cholesterol metabolism are strongly linked to neurodegenerative conditions. TMAO can therefore be considered a potential marker of Alzheimer's disease [23].

Amino acid metabolites

The microbiota is involved in amino acid catabolism, the products of which are involved in the production of inhibitory and excitatory neurotransmitters [3]. Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain is produced by many species of Lactobacillus and Bifidobacterium, via the metabolism of glutamate [25]. Decarboxylases secreted by Clostridium, along with Streptococcus, Escherichia, and Enterococcus spp are involved in the conversion of tryptophan into tryptamine which then participates in the release of serotonin by enteroendocrine cells and the enteric nervous system [23,25]. Norepinephrine is produced by, Escherichia, Bacillus, and Saccharomyces spp; dopamine is produced by bacillus and acetylcholine by lactobacillus [25].

Vitamins

Vitamins are essential nutrients involved in several bodily functions from energy processing to cell growth and cognitive development. Gut-derived vitamins are taken up from the colon as compared to dietary vitamins which are taken up from the small intestine, primarily the jejunum. Vitamin K is produced by Escherichia coli, Klebsiella pneumoniae, Propionibacterium, and Eubacterium; vitamin B2 (riboflavin) by Bacillus subtilis and E. coli; vitamin B9 (folic acid) by Bifidobacterium, Lactococcus lactis and Streptococcus thermophilus; and B12 (cobalamin) by Lactobacillus reuteri and Propionibacterium freudenreichii. Vitamin K being thrombotic is administered in neonates to prevent haemorrhagic disease prior to the development of their gut microbiome. Increased intake of vitamin K is linked to decreased complaints regarding subjective memory in the elderly [23].

Gut-brain axis

The bidirectional communication network between the gut microbiota and the brain, known as the gut-brain axis involves the CNS - neuroendocrine, the autonomic system, the enteric nervous system, and the gut microbiota. Through this complex network, the gastrointestinal tract can govern the functioning of the brain and vice versa (Figure 1).

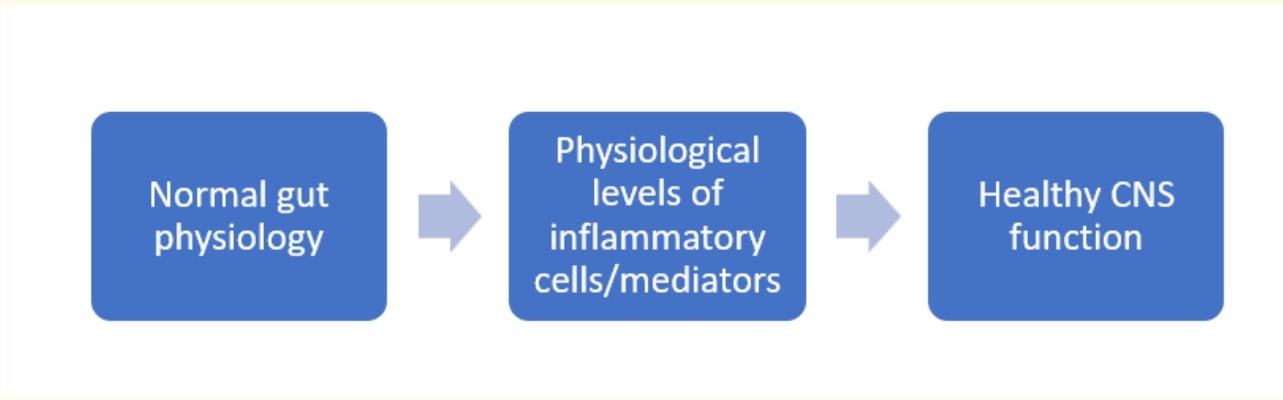

Figure 1: *The healthy gut-brain axis.*

Microbiota and the vagus nerve

The vagus nerve, the main component of the parasympathetic nervous system interacts with the gut microbiome and relays information to the CNS, directly activating the neurons of the brain. When this bidirectional connection is compromised due to a disturbance in the nerve, it may cause either CNS or GI disturbances.

When mice were administered a subclinical dose of *Campylobacter jejuni*, the were found to exhibit more anxiety like behaviour due to the activation of the neurons in the nucleus tractus solitarius. On the contrary, *Lactobacillus rhamnosus* was shown to be ineffective in treating anxiety and depression like behaviours in mice that had undergone vagotomy [22,25]. Vagal nerve stimulation has also been shown to improve the mental symptoms of intractable epilepsy [22]. It can therefore be considered a viable treatment option in CNS disorders.

Neuro and enteroendocrine signalling

The microbiota also interacts with the CNS via enteroendocrine cells (EEC), the sensory cells of the gut. EEC detects signals from the gut microbiota through TLRs, G- protein-coupled receptors and receptors for microbial by products like SCFAs, carbohydrates, amino acids, and peptides [25]. Upon binding to these microbial metabolites, EEC induces the release of peptide hormones; gastrin, ghrelin, GLP-1, and GIP and of neuropeptides; orexin, galanin, CCK, PYY, and serotonin which can then act locally on enteric neurons or activate neurons in the portal vein to transmit signals to the brain via the vagus nerve [23]. In addition to their functions in digestion and satiety, these peptides are also found to influence memory formation, behavioural and emotional changes [25].

Microbiota and stress response

The HPA axis and the sympathetic adrenomedullary (SAM) system are the primary components of stress response. When activated, the HPA axis stimulates the release of corticotropin releasing hormone (CRH) from the hypothalamus, which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then signals the adrenal cortex to secrete cortisol, which along with epinephrine and norepinephrine released by the adrenal medulla, governs our stress/fight or flight response. This is carried out by increased metabolic activity (glucogenesis, lipolysis), and immunosuppression [26].

Stress in utero and in the early stages of life has been implicated in impaired development of the HPA axis and dysbiosis. It is believed to change the gastrointestinal environment, making it susceptible to changes in microbial composition. These impairments go on to modulate different behavioural processes (depression, anxiety and abuse related), learning and memory [26] (Figure 2).

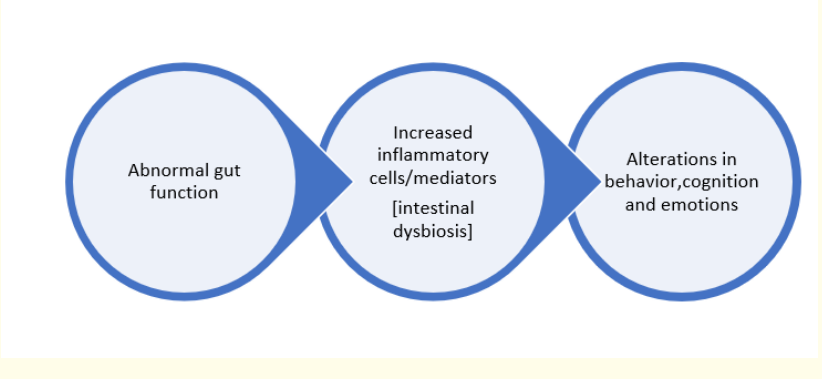

Figure 2: *The disturbed gut-brain axis leading to alterations in brain functioning.*

Gut microbes and diseases association

Gut microbes and stress

Many studies support the influence of gut microbes on stress and stress related behaviors. The association was established in animal studies, though recently many scientists started taking interest in this relation and had more human studies conducted. In an animal study, elevations in Plasma ACTH and corticosterone were higher in germ free (GF) mice than specific pathogen free (SPF) mice in response to restraint stress. Compared to SPF mice, GF mice also showed decreased brain-derived neurotrophic factor (BDNF) expression levels in cortex and hippocampus [1]. Another paper also suggests that gut microbiome plays a major role in neuroendocrine systems such as the HPA axis [2]. HPA is linked with cortisol that is closely related to stress and anxiety. Thus it can be a bridging gap between gut microbes and stress [19]. Multi-species probiotic capsule or Probiotic yoghurt had a positive effect on mental health and HPA axis in petrochemical workers [11]. Results of such mice studies concluded that gut microbiota plays a huge role in postnatal development of hypothalamic-pituitary-adrenal (HPA) response to stress [1-3]. There are little human studies to date. Chronic consumption (4 weeks) of fermented milk product with probiotics in healthy women induced reduced test related response and alterations in intrinsic activity of resting brain [4]. On administration of paraprobiotic *Lactobacillus gasseri* CP2305 in healthy young adults for 4 weeks, it improved chronic stress associated symptoms and sleep disturbance.

Gut microbes and anxiety

Anxiety disorder is one of the most common stress related disorder and it is itself a symptom for many psychiatric disorders. In a human study, intestinal gut microbiota's pattern changed significantly in patients with depression and anxiety [9]. By adjusting the intestinal flora through probiotics or non probiotic methods such as modulating dietary structures, there was an improvement in anxiety symptoms in most of the studies [7]. Suggestions on role of microbiota in behavior started after observations that gut microbiota dysbiosis is related to mental illnesses like anxiety and depression. As a result of many human and mice studies, gut microbe remodeling through use of antibiotics or probiotics were shown to improve anxiety like symptoms. Possible mechanisms include interference of gut microbes that can evoke signals that govern emotions and behaviour [8].

Gut microbes and depression

The discovery of bidirectional relationship between gut microbes and central nervous system led researchers to study role of microbiota in depression. Several studies in human subjects showed alteration in gut microbes in patients with depression compared to healthy patients [17,18]. Many human studies confirm administration of probiotics improves depression disorder. [10,12,13,20]. Like consumption of probiotics for 8 weeks in major depressive disorder patients had beneficial effects on insulin and Beck Depression Inventory [12]. Other study in older adults showed that probiotics induced improvement in brain function, increase in peripheral BDNF levels and slight reduction in inflammation. These findings suggested that gut microbiota may have a role in improving cerebral and cognitive functioning [13]. When a study was conducted to examine association between relative abundance of gut microbes and depression by consumption of flavonoid-rich juice in young adults, it was found out that flavonoid regulates gut microbiome. Thus, it helps and prevents in depression like symptoms [14]. An association between microbiota, depression and lower quality of life has been recently reported. Even nature related activities have an impact on diversity on gut microbiota, which can improve psychosocial behaviours of children [15,16]. It shows us how regulation of microbiota and its diversity is important in stress related disorders like depression.

Gut microbes and autism

Gut microbiota maintains a stable symbiotic relationship with human beings in the intestines, which are regarded as a "second brain" due to the number of genes encoded by intestinal microbes (i.e. 150 times the total genes of human cells). The gut-brain axis and its regulation by microbiota may play a key role in the biological and physiological basis of neurodevelopmental, and neurodegenerative disorders. Studies have shown that intestinal flora communicates with the brain via nervous system, the immune system and the endo-

crine system, which results in the shift of cognition, social behaviour, and emotion [27]. Autism spectrum disorder symptoms (ASD) is a severe neurodevelopmental disorder that is primarily characterised by various abnormal behavioural symptoms such as stereotyped behaviour, social interaction impairment, and restricted interests [28]. The etiology of ASD includes an interplay between genetic factors and environmental factors as well as both systemic inflammation and inflammation of the central nervous system [29]. Gastrointestinal symptoms, such as constipation, diarrhoea, abdominal bloating, pain on evacuation and vomiting have been reported in ASD patients [30]. It has been observed that microbiome dysregulation plays a very important role in the pathogenesis of inflammation which may contribute to manifestation of ASD symptoms [31]. On the basis of various studies, it has been analysed that participants with ASD had a lower abundance of *Bacteroides, E. coli, Bifidobacterium, Akkermansia*, and *Enterococcus,* a higher abundance of *Lactobacillus* and *Faecalibacterium* and a slightly increased abundance of *Ruminococcus* and *Clostridium*. It is possible that the reduced levels of beneficial bacteria combined with the increased levels of harmful bacteria results together to ASD symptoms. Several studies showed there was a higher level of *Clostridium* in individuals with ASD compared to controls and hypothesized that *Clostridium* can produce neurotoxins and contribute to ASD [32]. Probiotics supplements can protect the intestinal barrier and reduce effectively the occurrence of intestinal disease. It has been estimated that probiotics or their metabolites regulates changes in immune cells, cytokines and emotional behaviour and have great therapeutic effect. Hence, it is important to carry out more comprehensive studies to find further effective treatments.

Gut microbes and mood disorders

Humans have over 100 trillion bacteria, highly abundant in the intestinal tract.

The brain gut microbiota axis includes the CNS, neuroendocrine system neuroimmune systems, enteric nervous system or intrinsic nervous system, autonomic nervous system including the intestinal microbiota.

It has become evident in recent years that the gut microbiome and the brain communicate in a bidirectional manner, with each possibly affecting the other's functions, thereby having an impact on stress, anxiety, depression, and cognition. Gut bacteria manufacture about 95 percent of the body's supply of serotonin, which influences various mood disorders. Through this bidirectional communication system, signals from the brain can influence the physiological effects of the gut, including motility, secretion and immune function, and signals from the gut can influence the brain function with mood states.

Evidence linking between gut microbes and mood disorders suggests that intestinal microbiota is associated with the neuro-endocrine-immune pathways and can be associated with various mood disorders. This review summarizes findings from studies looking into neurobiochemical, neuroendocrine, and neuroimmune system mechanisms of the gut-brain axis to determine the relationship between intestinal microbiota and mood disorders [36]. Different intestinal microbiota can change the symptoms of mood disorders, meanwhile mood disorder itself can change the constitution of microbiota.

Disturbance in this bidirectional route of communication has showed relevance for various mood disorders.The altered gut microbiota composition in patients with depression was related to abnormalities in hypothalamic–pituitary–adrenal (HPA) axis function, intestinal low-grade inflammation and an imbalanced neurotransmitter metabolism via the brain–gut–microbiota axis [35].

Human health can have both positive and negative effects by the microorganisms living in the gut. Findings showed that microbial diversity and taxonomic compositions were significantly changed compared with healthy individuals [34]. A case study on the correlation between gut microbial alternation and mood swing of healthy adults was conducted in a closed human life support system during a 105-day experiment. A profile of mood states questionnaire was used to record the mood swings. Correlation between gut microbes and mood were identified. Results indicated that the composition of microbial community could play a role in emotional change in mentally physically healthy adults (37).Further understanding , gut bacteria produce many other neurotransmitters such as dopamine, norepinephrine, acetylcholine, and GABA, which are critical for mood disorders. The gut microbiome can cause changes in pattern of how our brains response and react (38). GABA has several well-known physiological and psychological functions. Different studies showed that it is present in the brain where it acts as a major inhibitory neurotransmitter in central nervous system.

Specifically, dysfunctions in GABA metabolism are involved in various mood disorders. Increased level of GABA in the human gut could be derived by the ability of the intestinal microbiota or ingested probiotic, such as bifidobacteria and lactobacilli, to metabolize dietary monosodium glutamate (MSG). Serotonin (5-HT) can produce some changes in cognitive functioning mood changes. Reduced 5-HT is associated with impaired long-term memory functioning. It may also impair cognitive functioning and improve attention. Its altered levels are also detected in many different psychiatric disorders. Increasing evidence indicates that human gut microbiome affects the functioning of how our brain works. The Relationship between the effects of the gut microbes emotions and behaviour.

Ingestion of certain probiotics affected memory and emotions by increasing GABA.The intestinal microbiota influences brain chemistry and behavior. Hence it is proved that Prebiotics have a relationship with mood disorders, but the relationship between the constitution of intestinal microbiota, probiotics and mood disorders has not reached a consensus.

Current research on gut microbiota and mood disorders is still at its early stage. Growing evidence shows change in gut microbiota in patients with mood disorders, which may play an important role in disease pathology.

Effects of probiotics on the gut-brain axis

As we have seen, the gut microbiota plays a major role in maintaining homeostasis and well-being. It can therefore be understood that changes in it's composition and functioning can affect several physiological processes, leading to disease progression.

The Gut Brain axis has been studied for many years now. The endeavor to understand how the gut microbiota - that is, all the microorganisms in the intestine, affect the various aspects of the brain - cognition, memory, response to stress, as well as their role in the many psychological disorders was done as early as the 1930s.

Today, we have evidence based on various mice-trials, as well as some human studies that there is indeed a strong link between the gut and the brain.

We have begun understanding the physiology behind how exactly the link between the microbiota and various psychological disorders works - and from that many derivations on the thinking process and brain changes have been made. While there is yet much to be understood on the specific mechanisms behind this link, a lot of headway has been made in utilizing the current understanding of this link to manipulate various mental process.

One such effort to use this understanding of the gut-brain axis, is the use of probiotics and other health substitutes, to manipulate the gut microbes and study the effects of this manipulation on the brain.

Probiotics are beneficial bacteria that yield positive health benefits and prebiotics are compounds, that, when fermented in the gut, produce specific changes in the activity and composition of gut bacteria. The term psychobiotics was coined to define probiotics and prebiotics, that when consumed in appropriate quantities, yield positive psychiatric effects. This review documents the current research on effects of psychobiotics on mental processes [40].

A randomized controlled trial was conducted to investigate the effects of probiotics on patients with clinical depression [39]. The trial studied the effects of multi-strain probiotics vs placebo along with antidepressants on 47 patients (N probiotics = 21, N placebo = 26) over a period of 31 days. Neither the researchers, nor the participants knew which preparation was given to the subjects. The results of the study showed that there was a greater improvement of symptoms in the probiotic group as compared to the placebo group. There was a temporary change in the intestinal flora. At the end of the study, there was an increase in the lactic acid bacteria - this was linked to an improvement in the depressive symptoms. The study showed another interesting effect in relation to brain activity. In patients with depression, certain brain regions for emotional processing behave differently than in individuals with good mental health. After four weeks of probiotics, fMRI scans showed that this brain activity had normalized in the probiotic group but not in the placebo group.

Another randomized double blind study provided evidence that consumption of probiotics improved mood in a generally healthy sample [40]. 55 healthy male and female volunteers consumed either a mixture of probiotics (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum*) or a placebo over 30 days. At the end of the trial, the volunteers completed a range of self-report measures on mood and distress. The participants of the study were also required to collect 24 hour urine samples before and after the intervention. This allowed for the assessment of cortisol levels.

The volunteers who were treated with probiotics showed significant declines in self-reported negative mood and distress as compared to the placebo group. This result was further compounded by the fact that the probiotic group had a decrease in the urinary free cortisol levels - which indicated a decrease in stress levels [40].

Another randomized double blind study- further proved that manipulation of the gut microbiome using probiotics modified emotional and cognitive behavior - which can be linked back to the thinking process [41]. This study included three groups - probiotic group, placebo group and no intervention group- each with 15 participants. The study period was 4 weeks. The results showed that - the probiotic group had a significant increase in positive effect and blunting of vulnerability to depression. It also showed that Probiotics improved memory performance and altered brain activation patterns.

In conclusion, based on all the data from these clinical trials that exists today, it is clear that the intake of probiotics and the resultant changes in the microbial environment of the gut has a definitive link to mental process that cognition, emotional responses as well as efficacy in treating certain psychological disorders. There is hope that further research into this field will alter the course of treatments for many psychiatric disorders [40,41].

Discussion

Available studies that are involved in psychiatric disorders relation with gut microbiota in evidence of affecting the etiology and pathophysiology mechanism of psychiatric disorders. Studies contributing the effect of gut microbiota on many psychiatric disorders had proved the thought of impact of this relation. Gut microbiota had been under studies in understanding psychiatric disorders mainly due to the absence of understanding psychiatric disorders etiology and pathophysiology.

Involved studies in this relation had been done on many psychiatric disorders separately. This dividing of disorders that each psychiatry disorder has its own clinical studies mainly for accuracy of the results. Studies involved in BD and MDD was detected common feature in gut microbiota changes. Gut microbial diversity and composition changes are the most found changes in mood disorders. Additional studies involved in gut microbiota effect on psychiatric studies had shown elevation of Actinobacteria, *Enterobacteriaceae* and reduce in *Faecalibacterium* in depression most commonly. These results had been confirmed by comparing them with control studies. The data of the relation between gut microbes and individual psychiatric disorders is summarized below. [table 1].

Contributing these studies, many clinical studies had used these studies beside its confirmation of the results, they had used them as a diagnostic biomarker in order to differentiate between psychiatric patients and healthy individuals compared with healthy control studies. This thought had been confirmed its impact in distinguish between healthy patients and psychiatric patients.

Result

Gut microbiota studies that involved in psychiatric disorders discovery in etiology and pathogenesis mechanism had shown variety of results in each disorder. Many studies had involved in relation between gut microbiota and understanding psychiatric disorders had experiments in animal models, healthy individuals and patients with psychiatric disorders compared with healthy individuals. Additional to that any changes detected were similar in many psychiatric disorders. Effect of dietary food, treatments and environment had shown great impact in the relation study between gut microbiota and its etiology in psychiatric disorders.

Psychiatric disorders	Effects	Gut microbiota
Stress	Plasma ACTH and corticosterone are both high Decreased brain-derived neurotrophic factor (BDNF) expression levels in cortex and hippocampus.	*Lactobacillus gasseri* Bacteria
Anxiety	Improvement in anxiety symptoms	The intestinal flora
Depression	Improvement in brain function, increase in peripheral BDNF levels and slight reduction in inflammation.	Flavonoids
Autism	Constipation, abdominal bloating, pain and vomiting	Intestinal flora and *Clostridium*
Mood disorders	Changes mood regarding the percent of increase intestinal microbiota as it affects neurotransmitters that have major role in mood behaviour changes	Intestinal microbiota

Table 1: *Gut microbiota and their effect in different psychiatric disorders.*

Studies involved in this relation with ASD had shown many changes in behaviour in these patients regarding diagnostic biomarkers. Besides that, probiotics had improved behavioural measures in psychiatric disorders. Additional to that, a reduce of *Bacteroides, E. coli, Bifidobacterium, Akkermansia* and *Enterococcus*, an increase of *Lactobacillus* and *Faecalibacterium*, and a slightly increased abundance of *Ruminococcus* and *Clostridium* was detected on ASD.

Mood disorders with its variety like MDD and schizophrenia had shown many changes compared to control group. The understanding of this relation in mood disorders was challenging regarding the fact of different intestinal microbiota can change the symptoms of mood disorders, meanwhile mood disorder itself can change the constitution of microbiota. But treatments and probiotics had shown great impact in control of mood disorders.

Concluding the results of the relation between gut microbiota and its etiology with pathophysiology mechanism understanding in psychiatric disorders have great hope in understand more about many psychiatric disorders. Additional to that, these studies had helped in discovery of many ways in control behaviour and symptoms by the facts the results in these studies.

Conclusion

Current available studies involved in understanding the etiology and pathogenesis of psychiatric disorders had contribute the understanding to gut microbiota cause. Regarding the results of clinical studies, gut microbiota had shown its effect and impact in many psychiatric disorders. Beside this fact, it has been used as diagnostic tool and biomarkers in diagnosis of psychiatric disorders. Additional to that, clinical studies had great impact in differentiate between psychiatric disorders and healthy people. This review paper opens the gate for the study of a specific association between microbes and psychiatric disorders. This not only gives us a new method of treatment but also gives us ways of screening the various psychiatric disorders.

Author Contributions

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Volume 12 Issue 4 April 2023