Gut Microbiota And Depression: Insights Into The Probable Link Between The Two

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

For this review paper, no human or animal samples were tested.

Abstract/ Executive Summary

The gut microbiota plays a crucial role in maintaining health and strengthening immunity .These microflora are said to be beneficial for psychological wellness.. It has been established that the gut microbiota and the brain have a bidirectional relationship. Numerous studies have demonstrated the importance of microbiota in the growth of brain systems.. There is compelling evidence that the microbial population residing in the gastrointestinal tract correlates with the development of psychological and anxiety disorders.This offers scientists a new avenue to explore in order to find treatments for resistant and relapsing patients of MDD.This review provides important insights into the relationship between gut microbiota and depression. The paper particularly highlights relevant research as well as preclinical and clinical trials that point towards an association between depression and gut microbiota.

Keywords: Depression; Depressive disorders; Gut microbiota; Gut-Brain axis (GBA); Microbiota-Gut-Brain axis (MGB); Microbial diversity.

Dedication (Optional)

Dedicated to all the patients diagnosed with depression

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List of Acronyms

MDD	Major Depressive Disorder
GI tract	Gastrointestinal tract
ENS	Enteric Nervous System
CNS	Central Nervous System
ANS	Autonomic Nervous System
SSRIs	Selective Serotonin Reuptake ISnhibitors (SSRIs)
SNRIs	Selective Norepinephrine and Serotonin Reuptake Inhibitors
MAOIs	Monoamine Oxidase Inhibitors
MDE	Major Depressive Episode
DM	Depression Mood
DSM-5	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
DMDD	Disruptive Mood Dysregulation Disorder
PDD	Persistent Depressive Disorder
PMDD	Premenstrual Dysphoric Disorder
TCAs	Tricyclic antidepressants
OCD	Obsessive-Compulsive Disorder
GAD	Generalized Anxiety Disorder

PTSD	Post-Traumatic Stress Disorder
SCFAs	Short Chain Fatty Acids
GALT	Gut-Associated Lymphoid Tissues
GBA	Gut-Brain Axis
FGID	Functional Gastrointestinal Disorders
IBS	Irritable Bowel Syndrome
GABA	Gamma-Aminobutyric Acid
HPA axis	Hypothalamic-Pituitary-Adrenal axis
MGB axis	Microbiota-gut-brain axis
IL	Interlukin
TNF	Tumour Necrosis Factor
GMB	Gut microbiome
HC	Healthy Controls
BDNF	Blood-Derived Neurotrophic Factors
LH	Learned Helplessness
CSDS	Chronic Social Defeat Stress
FMT	Fecal Microbiota Transplantation

Chapter 1

Introduction

1.1 Background

Depression is a widespread, debilitating, and pervasive public health concern (World Health Organization: WHO & World Health Organization: WHO, 2021). It is described as possessing a weak emotional outlook, losing optimism, and becoming apathetic (Truschel, 2022). Under the World Health Organization (WHO), major depressive disorder (MDD) is the biggest contributor to the burden of disease worldwide (Zheng et al., 2016). Roughly 280 million individuals nationwide grapple with melancholy (World Health Organization: WHO & World Health Organization: WHO, 2023). MDD strikes roughly 7% of individuals over a year, with significant age-bracket variations. Compared to people 60 years of age and older, the frequency is three times higher in people aged 18 to 29 (Chand, 2023). Females have 1.5-3 times more instances of depression onset than boys embarking on their adolescence. The approximate digits of adults in the US who battle depression is just shy of 17 million, but the actual figure is substantially understated because many of them have not even sought treatment (Chand, 2023). Intricate connections between factors that are biological, social, and psychological are among the underlying causes of depressive symptoms (World Health Organization: WHO, 2019). The idiosyncrasies, together with physical and psychological changes, can substantially impair functional capacities and even result in homicide (World Health Organization: WHO & World Health Organization: WHO, 2023). Patients with despair experience skeptical results due to the condition's frequently occurring recurrences and remissions, which degrade the quality of life (Website, 2023).

The gut microbiome, an expansive and evolving array of microbes existing in the alimentary tract of humans, has an enormous influence on the host during physiological equilibrium and

ailment (Thursby & Juge, 2017). The GI tract is one of the greatest interfaces (250–400 m2) between the host, external variables, and internal antigens in the human body (Thursby & Juge, 2017). Genetics, advancement and growth, and geographic location greatly influence individual variations in the components of the intestinal flora (Bates, 2017).

The gut microbial diversity have been demonstrated to be substantially correlated with behaviors that relate to the state of mind (Winter et al., 2018). As claimed by Winter et al. (2018), this link is the result of a freshly described bilateral interaction between the gut and the cerebrum, which is carried out by sensory, neuroimmune, and neuroendocrine neuronal channels, and so alterations that affect one organ will have consequences for the other's functionality. This constitutes the microbiota-gut-brain axis because abnormalities in the overall makeup and abundance of gut microbes may interfere with both the enteric nervous system (ENS) and the central nervous system (CNS) (Zhu et al., 2017). According to Zhu et al. (2017), the CNS, the autonomic nervous system (ANS), and the ENS essentially co-dominate the intestinal lumen. Microbial dysbiosis, which is linked to MDD, is characterized as a discrepancy in microbial diversity brought on by the disruption of the microbiota's delicate balance and the ensuing functional alterations (J. Liu et al., 2022). A recently published comprehensive analysis by Pouranayatihosseinabad et al. (2023), and J. Liu et al. (2022) found a link between administering antibiotics and later developing depressive symptoms. Perhaps, the main reason for this is that antibiotics decrease the spectrum of the microbes in the gut (Guida et al., 2018).

Clinical investigations have shown that a significant fraction of depressed individuals do not experience a satisfying therapeutic response with their initially attempted therapy effort, nor do they succeed with follow-up treatments (Rush et al., 2003). Antidepressant drugs and psychotherapy are included as first-line treatments in the majority of guidelines that recommend successful treatments (Cuijpers et al., 2020). Although some patients respond

well to the aforementioned therapies, there is still much potential for advancement. Cuijpers et al. (2020) mentioned that over the past few decades, over 600 clinical trials have evaluated the effectiveness of psychotherapies for depression, and more than 500 randomized trials have examined the effects of antidepressant drugs (although relatively few are undertaken for early-onset melancholia). A minor risk of bias exists in less than 20% of drug trials and less than 30% of therapy trials, which leaves the results questionable (Cuijpers et al., 2020). Regardless of alternative approaches that include interpersonal psychotherapy and non-pharmacological therapies like electroconvulsive therapy, the specific requirements of many crestfallen patients remain unmet due to despair that is tolerant to therapy and tardy onset of initially prescribed antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) (Beurel et al., 2020). An innovative approach that emphasizes the relationship between the encephalon and gut microbiota may aid in the mellowing of novel antidepressant panacea. A crucial question that has to be answered is the linkage of the connection involving both of these, which will aid in helping to comprehend the function that the gut microbiota possesses in depression. Winter et al. (2018) have shown a significant association between the intestinal microbiome and depressive disorders. Thereby this review paper delves into the significance of the gut microbiota on depression therapy and how it impinges on mental health.

1.2 Aims and Objectives

This comprehensive literature review aims to to shed light onto the correlation between the gut microbiota and occurrence of depression and how these gut microorganisms correspond to depression in light of all the data highlighted in the research on the microbiome of the digestive tract and depressive disorders.

1.3 Methodology

This paper was composed utilizing recently published journals, research papers, and articles; all relevant data was gathered from PubMed, Google Scholar, Atlas Biomed, National Library of Medicine, Nature Reviews Neuroscience, frontiers, De Gruyter, Cureus; additional data was gathered from Cleveland Clinic, Verywell Mind, Pharmacology Education Project, RxList, NHS inform, Drugs.com, UpToDate, Science Direct. Certain terms and definitions were gathered from Google; the majority of the material was drawn from the last five years' worth of articles and journals, but also included information from the previous 10-15 years to enhance the review paper.

1.4 Depression

1.4.1 Definition, indications, and risk factors

Depression is a mood illness that results in ongoing melancholy and dissatisfaction. Disruptive Mood Dysregulation Disorder (DMDD), Major depressive disorder or Clinical depression, Persistent Depressive Disorder (PDD/dysthymia), and Premenstrual Dysphoric Disorder (PMDD) due to other medical condition are the categories under which depressive disorders are categorized in the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association (Depression: Causes, Symptoms, Types & Treatment, 2022). All demoralizing conditions have symptoms of melancholy, nothingness, or irritation along with physical and mental changes that significantly impair the individual's capacity for functioning. In the population as a whole, bleakness is a prominent psychological condition 10% over the course of a lifetime, with a potential 20% frequency in medical facilities (Tolentino & Schmidt, 2018).

Indications

According to the DSM-5, a Major Depressive Episode (MDE) cannot be diagnosed unless no fewer than five indications have persisted for two weeks in a row (Truschel, 2022). At the very least, one of the manifestations ought to indicate anhedonia or depression. (Tolentino & Schmidt, 2018). The secondary ones include alterations in appetite, sleeplessness or excessive sleepiness, psychomotor disturbances or developmental delays, exhaustion or lethargy, cognitive incapacity or excessive guilt, feeling unimportant, and thoughts about committing suicide (Tolentino & Schmidt, 2018).

Risk factors of depression

As claimed by Depression, (2023) numerous genetic, psychological, and environmental variables, as well as others, may contribute to despair. Potential risk factors of depression include inheritance and hereditary factors, persistent stress, traumatizing past, some character qualities, such as possessing low regard for oneself and being too reliant, crucial, or detrimental, and having complicated or unpleasant circumstances, such as sexual or physical misconduct, the losing of a relative and so forth (Depression, 2023).

1.4.2 Types of depression

The table below shows different types of depression according to DSM-5

Depressive disorders	Definition
Clinical depression	Defined as the diagnosis of severe depressive disorder that indicates that the patient had a lack of interest in recreational pursuits, or a change in satiety, in addition to the patient feeling exhausted most days for at least two weeks. This is both the most severe and most prevalent kind of depressive illness.
PDD	PDD is the medical term for mild to moderate depression that continues for a minimum of a year or two. Compared to major depressive illness, the indications are less severe. PDD was formerly referred to as dysthymia by medical professionals.
DMDD	In young children, DMDD results in repeated episodes of extreme annoyance and persistent disruptive behavior. In most cases, symptoms appear around the age of 10.
PMDD	PMDD is characterized by mood prognostics, such as abrupt changes in attitude, jitters, agony, and premenstrual syndrome (PMS) symptoms. These symptoms typically disappear after the menstrual cycle starts within a few days, but they occasionally can be so severe that they substantially disrupt the patient's day-to-day existence.
Depression caused by a different medical condition	Numerous medical problems might alter the physical appearance in ways that lead to sentimentality. Hypothyroidism, heart disease, Parkinson's disease, and cancer are a few examples. When the underlying issue is addressed, depressive behavior also gets better.

Table 1: Depressive disorders are grouped as follows in the DSM-5 by the American Psychiatric Association (Professional, 2023)

According to Professional (2023), Major depressive illness may take on several forms in conjunction with:

Seasonal Affective Disorder (Seasonal Depression)	Seasonal depression is a form of major depressive disease that normally develops in the months of fall and winter and subsides in the warmer months of the year.
Prenatal Depression and Postpartum Depression	Depression during pregnancy is referred to as prenatal depression, as is depression after labor and delivery. Depression that appears within four weeks following childbirth is known as postpartum depression. As claimed by the DSM, they are "major depressive disorder (MDD) with peripartum onset.
Atypical depression	This ailment, often referred to MDD with atypical characteristics, has symptoms that are a little different from those of "typical" depression. The primary distinction is a brief shift in mood in reaction to a joyful event (mood reactivity). Increased hunger and risk of rejection are two additional significant symptoms.

Table 2: Other forms of Depressive disorders In the opinion of DSM-5

In addition to possessing manic or hypomanic periods, people with bipolar illness also suffer depressive episodes (Depression: Causes, Symptoms, Types & Treatment, 2023).

1.4.3 Current treatment options for depression

Irrespective of the extent to which a person's dejection is, recovery should involve developing innovative abilities in particular tackling issues and modifying one's lifestyle to reduce anxieties, fostering workout and physical wellness, and abstaining from alcoholic beverages and other substances. In the report of Cuijpers et al. (2020) for depressive disorders, numerous therapeutic options consist of medicine, counseling, and general therapies in particular calming techniques. As claimed by Ley et al. (2011), an alternative is to observe to see if the symptoms fade away afterward without therapy and if the mood disorder is mild or has recently commenced. However, this "watchful patiently awaiting" tactic does not imply that the indications are overlooked (Ley et al., 2011). Considering the warning signs of moderate or severe depression can linger for a long time and are quite concerning it is typically crucial to seek prompt treatment (Ley et al., 2011). The different categories of depression therapies attainable are psychiatric interventions, antidepressants, herbal remedies, sleep deprivation therapy, and electroconvulsive therapy (Institute for Quality and Efficiency in Health Care (IQWiG), 2020).

1.5 Antidepressants

1.5.1 Neurotransmitters related to antidepressants

In the opinion of Sheffler (2023), neurotransmitters are chemical agents that transport, reinforce, and balance information between target cells all across the entire organism and neurons. Our brains continually control everything from breathing to heartbeat to learning and attention levels with the help of billions of neurotransmitter molecules and various psychological processes including dread, psychological state, relaxation, and joy might also be affected by them Sheffler (2023). Acetylcholine, glutamate, GABA, glycine, dopamine, norepinephrine, and serotonin are a few instances of these neurotransmitters that frequently

circulate in the cerebrum and body (Sheffler, 2023). In assent with Schimelpfening, (2022) the monoamines are a group of three fundamental chemicals that are thought to have a role in controlling mood. These largely serve the function of brain chemicals, which deliver nerve impulses to the brain's appropriate receptors (Schimelpfening, 2022). These neurotransmitters, which antidepressants also interact with, include:

Dopamine: According to Sheppard, (2023) dopamine is a specific sort of neurotransmitter found in the brain that regulates several bodily processes, including motivation, mood, focus, and memory. It additionally possesses hormonal effects (Sheppard, 2023). As stated by Sheppard, (2023) any individual who suffers from dopamine complications may perceive a loss in neurocognitive abilities, such as concentration, memory, and decision-making abilities. Dopamine is linked to many psychiatric disorders, much as the neurotransmitter serotonin, which helps regulate temperament (Sheppard, 2023).

Noradrenaline: Norepinephrine, additionally referred to as noradrenaline, is a neurotransmitter in the CNS that is mostly stored in the sympathetic nervous system's neurons, however, traces are also kept in the tissue of the adrenal glands, which lie atop the kidneys (Purse, 2020). As claimed by Professional (2023), this chemical is a neurotransmitter that plays a crucial part in consciousness and the body's fight-or-flight response.

Serotonin: Serotonin, a 5-hydroxytryptamine or 5-HT is a monoamine neurotransmitter that exists naturally in the body and is crucial for many bodily and mental processes, including sleep, mood regulation, learning, memory, and cognition (Salters-Pedneault, 2023).

1.5.2 Classification of antidepressants

According to Salters-Pedneault (2023), Tricyclic antidepressants (TCAs), SSRIs, SNRIs, monoamine oxidase inhibitors (MAOIs), and atypical antidepressants are the main types of antidepressant medications that are shown in the table below:

Classes	Indication	Mechanism of Action	Side Effects
TCAs	Moraczewski (2023) states TCAs treat mild to severe despair. Besides these are fairly effective in alleviating acute and treatment-resistant depression (Von Wolff et al., 2013). Also contributes to alleviating migraines, obsessive-compulsive disorder (OCD), concernment, sleep disorders, and persistent pain relief.	Are employed to prevent serotonin and norepinephrine from being reabsorbed in the presynaptic terminals, which boosts the degrees of neurotransmitters in the cleft of synaptic neurons (Moraczewski, 2023).	Retinal blurring, throat dryness, bowel issues, mass fluctuations, hypotension when stood up, breakouts, and tachycardia (Tricyclic Antidepressants (TCAs) Drugs: List, Side Effects, 2021).
SSRIs	Bulimia, agoraphobia, and panic disorder, alongside different significant phobias, generalized anxiety disorder (GAD), OCD, panic disorder, severe phobias, such as agoraphobia and social phobia and post-traumatic stress disorder (PTSD) (Selective Serotonin Reuptake Inhibitors (SSRIs), 2023)	In the opinion of Chu (2023), serotonin activity is boosted by SSRI action, which suppresses the reuptake of serotonin.	Erectile dysfunction, fainting, and tremors are some of the common side effects (Selective Serotonin Reuptake Inhibitors (SSRIs), 2023).

Classes	Indication	Mechanism of Action	Side Effects
SNRIs	Treat maladies, particularly anxieties and persistent pain, particularly nerve-related agony (Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), 2019).	SNRIs restrict serotonin and norepinephrine from being reabsorbed by the neurons in the brain (Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), 2019).	Erectile dysfunction, perspiration, exhaustion, mouth dryness, headache, sleeplessness, nausea, constipation, and reduced calorie intake (Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), 2019).
MAOIs	Grief, fret, uneasiness (List of MAO Inhibitors + Uses &Amp; Side Effects, 2023).	Norepinephrine, serotonin, and dopamine are neurotransmitters that escape the nervous system through an enzyme called monoamine oxidase (MAO) and because MAOIs hinder this from transpiring, a greater quantity of these brain chemicals are accessible to alter depressed-related shifts in both cells and pathways (Monoamine Oxidase Inhibitors (MAOIs), 2019).	Oral irritation, diarrhea, insomnia, dizziness, allergic reaction where a patch was positioned on the skin, uncontrollable muscular tremors, hypotension, decreased libido, troubled urine flow, achy muscles, Paresthesia (Monoamine Oxidase Inhibitors (MAOIs), 2019).
Atypical Antidepressants	Serious depressive patients who don't respond well to SSRIs after initial treatment or experience too many side effects (UpToDate, 2023).	Atypical antidepressants alleviate depression by eventually leading to changes in brain chemistry and communication in the neural network that is known to govern temperament (Atypical Antidepressants, 2019).	Problems with stool, a higher risk of diarrhea, mouth irritation, feeling lightheaded, and a spike in satiety (Atypical Antidepressants, 2019).

Table 3: Classes of antidepressants provided with indication, mechanism of action, and side effects

1.6 Gut microbes

1.6.1 Introduction to gut microbes

The gut microbiota, a diverse and dynamic population of microorganisms found in the human GI tract, has significant influence on the host during homeostasis and ailments (Thursby & Juge, 2017). As claimed by Bäckhed et al. (2005), the phrase "gut microbiota" refers to the assortment of bacteria, archaea, and eukaryotes that colonize the GI tract and evolved alongside the host for thousands of decades to develop an extensive and beneficial interaction. The colony of microbes known as the gut microbiota lives in the gastrointestinal system in a mutualistic interaction with hosts and more than 1014 microorganisms are thought to reside in the GI tract, which has around 10 times as many bacterial cells as human cells and more than 100 times as much genetic material as the human genome (Thursby & Juge, 2017). the existence of nation-specific microbial signatures indicates that nutrition and other environmental variables, as well as likely host genetics, influence the genetic makeup of the gut flora (Li et al., 2014) . For the physiological wellness of hosts, the gut community, a group of bacteria that inhabit the gastrointestinal system, supplies essential signaling metabolites (Li et al., 2014). In a healthy state, the metabolites produced by the gut microbiota assist in maintaining the fundamental bodily functions of the hosts, but when this process is disturbed, it can result in a wide range of illnesses, including cancer, diabetes, cardiovascular disease, intestinal ailments, and metabolic disorder (Li et al., (2014).

1.6.2 Role of the human microbiota

Research indicates that the microbiota serves the host in a variety of physiological ways, including boosting gut integrity, shaping the intestinal epithelium, generating energy, warding off infections, and controlling host immunity (Thurs and Juge, 2017). The altered

microbial composition known as dysbiosis, however, has the potential to disrupt these systems (Chang & Lin, 2016). The gut microbiota offers a variety of advantageous features to the host on account of its substantial genetic content and metabolic balance. For instance:

Maintaining a symbiotic relationship: The microorganisms residing in the gut have some of the most crucial functions in maintaining the mucosal barrier's integrity, supplying nutrients including vitamins, and defending against infections (Thursby & Juge, 2017). Thursby and Juge (2017) cite a strong immune system that depends on the interaction of the mucosal immune system with commensal bacteria. In a healthy body, the gut microbiota contributes significantly to the metabolic, immune, and gut protective processes by maintaining a symbiotic interaction with the gut microbiota, which receives nutrients from host food components and sheds epithelial cells, is an organ in and of itself with significant metabolic potential (Sonnenburg et al., 2005).

Supplying nutrients: As reported by Thursby and Juge (2017), dietary carbohydrates are a major source of nutrition for the gut flora. Colonic organisms in particular Bacteroides, Roseburia, *Bifidobacterium*, *Fecalibacterium*, and Enterobacteria generate inedible oligosaccharides and carbohydrates that escape near-breakdown through stir, which results in the production of short-chain fatty acids (SCFA), such as butyrate, propionate, and acetate, which are plentiful origin of power for the host (Thursby & Juge, 2017). It is thought that the SCFAs (Short Chain Fatty Acids) ligand-receptor interaction with the G protein-coupled receptor Gpr41 mediates the host energy balance (Macfarlane & Macfarlane, 2003).

Drug and foreign substances metabolism: Because hepatic sulfotransferases are competitively inhibited, recent research by Clayton et al. (2009) has shown that the gut microbial metabolite p-cresol may decrease the liver's ability to metabolize paracetamol. The common bacterium *Eggerthella lenta* from the *Actinobacteria* phylum has recently been

demonstrated to enhance a cytochrome-containing operon, inhibiting cardiac glycosides in particular digoxin (Saha et al., 1983). The microbial-glucuronidase-induced deconjugation of the anticancer medication irinotecan, which can contribute to its toxicities such as diarrhea, inflammation, and anorexia, is another intriguing example of microbiome-induced drug metabolism (Wallace et al., 2010).

Antimicrobial resistance: The gut mucosal immune system must be tolerant of the helpful commensals while preventing the proliferation of the resident pathogens since a healthy gut microbiota is necessary for optimal homeostasis (Johansson et al., 2008). The two-tiered mucus layer, which is mostly found in the large intestine and serves as one of the most basic antimicrobial defensive systems, prevents luminal bacteria from coming into touch with the epithelium (Thursby & Juge, 2017). The multitude of mucin glycoproteins that make up mucus are released by intestinal goblet cells and may stretch up to 150 μm from the colonic epithelium (Kim & Ho, 2010).

Immunomodulation: Immunomodulation is interpreted as the supervision and variation of the body's defence, which can be accomplished through immune response boosting or diminution (Herbal Biomolecules in Healthcare Applications, 2022). Coupled with the innate and adaptive immune systems, the gut microbiota supports gut immunomodulation (Jandhyala et al., 2015). The gut-associated lymphoid tissues (GALT), effector and regulatory T cells, IgA-producing B (plasma) cells, Group 3 innate lymphoid cells, as well as localized dendritic and macrophage cells in the lamina propria, are immune system components and cell types that take part in the immunomodulatory process (Jandhyala et al., 2015).

Maintaining the gut barrier: The transcription factor angiogenin-3, which has been linked to the formation of intestinal microvasculature, is induced by the gut microbiota and

plays a role in the structural development of the gut mucosa (Jandhyala et al., 2015). As stated by Jandhyala et al., (2015) the mucosal glycosylation patterns, which serve as microbial anchors at both the cell surface and intracellular levels, may also be modified by the gut microbiota. The expression of the carbohydrate moiety fucose on the cell surface glycoconjugates, for instance, may be stimulated by a signaling molecule released by the bacterium *Bacteroides thetaiotaomicron* (Jandhyala et al., 2015).

1.6.3 How does the gut microbiota affect certain medications?

Pharmacomicrobiomics describes the impact of microbiome divergences on drug/xenobiotic response and distribution (Dikeocha et al., 2022). Aziz, 2018 asserts that the fundamental idea behind pharmacomicrobiomics is the systematic investigation of interactions between drugs and the gut microbiota. More specifically, it is the study of how intra- and inter-individual microbiome changes impact medication action, temperament, efficacy, and toxicities (Aziz, 2018). Aziz, 2018 states that the human body's metabolic processes, defense mechanisms, and behavioral traits are all greatly influenced by the microbiome and this may also have an impact on how drugs are metabolized. The influence of the intestinal microbiota on medication metabolism and effectiveness has been investigated since the 20th century, and results have shown that it may either stimulate, inactivate, or increase the toxicity of pharmaceuticals and xenobiotics (Dikeocha et al., 2022). The biotransformation of pharmaceuticals by the gut microbiota may have a direct impact on how they are metabolized via a variety of mechanisms, including hydrolysis, demethylation, deamination, and reactive reactions (Dikeocha et al., 2022). Pharmaceuticals might alter the diversity of gut bacteria, and the variety of gut microorganisms can influence therapeutic effectiveness by changing the bioavailability and bioactivity of medicinal products (Wan & Zuo, 2022).

1.6.4 Gut-Brain Axis (GBA)

The central and enteric neural systems communicate in either direction via the GBA, which connects the brain's emotional and cognitive regions to the peripheral functions of the intestine. Recent scientific developments from Carabotti (2015) have highlighted the significance of gut bacteria in affecting these relationships. Via signaling from the gut microbiota to the brain and vice versa via neurological, endocrine, immunological, and humoral linkages, this relationship between microbiota and GBA seems to be bilateral (Carabotti, 2015). An advanced interaction system as reported by Carabotti (2015) guarantees the appropriate maintenance of gastrointestinal homeostasis and has been revealed through insights into the gut-brain interchange, this system is also anticipated to have numerous implications on sentiment, motivation, and higher cognitive processes. The term "gut-brain axis" encompasses the intricacy of these connections (Carabotti, 2015). The mechanism of GBA is shown in the figure below.

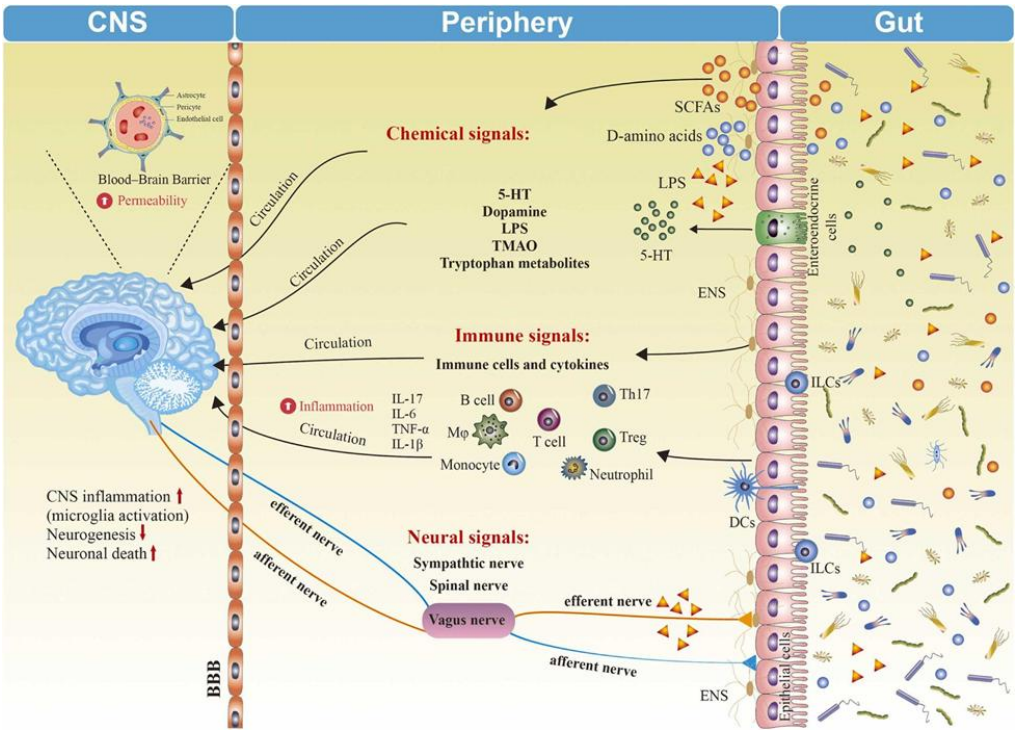

Fig.1. The mechanism of operation of the gut-brain axis in the body is shown. The CNS, the peripheral, and the gut are illustrated as the three main axes of the brain-gut-microbiota axis. Changes in this network result in intricate interactions between organs via direct nerves and systemic circulation routes, which affect the body's stability. Depression can be brought on by changes in the gut microbiota's composition and the SCFAs, D-amino acids, and intermediates produced by the microbiome. The CNS controls peripheral organs and tissue through neuronal regulation, neurotransmitters, immunological signals, and other elements in response to various signal reflexes, all of which contribute to appropriate bidirectional brain-gut axis signaling. Stress can upset this balance, which can lead to depression or other illnesses. CNS, Interleukin 6 (IL-6), Interleukin 17 (IL-17), Interleukin 1 (IL-1), Innate Lymphoid Cells (ILC), Lipopolysaccharide (LPS), Short Chain Fatty Acid (SCFA), Trimethylamine N-oxide (TMAO), and Tumour Necrosis Factor (TNF-) are some other common inflammatory cytokines. A few of the figure's components were created utilizing resources from Freepik.com. Extracted from Chang et al. (2022).

Numerous mechanisms, such as the vagus nerve, the defense system, the ENS, or the metabolizing processes of gut bacteria, may affiliate the brain and the gut (Zhu et al., 2017). Through the vagus nerve, the gut and cerebral are linked together neurally, and bacteria can trigger ENS afferent neurons through this pathway (Forsythe et al., 2014). Through the metabolism of numerous chemicals, gut microbes can also influence how the encephalon works. Zhu et al. (2017) stated that 95% of serotonin is synthesized in the gut, and gut microbes are crucial for serotonin synthesis, which is one of the climacteric neurotransmitters relating to cognition. The purpose of this organ is to keep an eye on and integrate gut processes while also connecting the brain's emotional and cognitive regions to peripheral intestinal processes and mechanisms including permeation of the intestinal tract, enteric impulse, activation of the immune system, and entero-endocrine signaling (Rhee et al., 2009).

Role of gut microbiota in GBA: Carabotti (2015) stated that the enteric microbiota is thought to have a significant role in GBA, interacting not only locally with intestinal cells and the ENS but also directly with the CNS via neuroendocrine and metabolic pathways. Over twenty years ago, the observation of the often significant improvement in hepatic encephalopathy patients after the use of oral antibiotics provided the strongest human evidence of a gut-microbe-brain connection (The Treatment of Chronic Hepatic Encephalopathy, 1991). Meanwhile, mounting evidence points to the influence of the microbiota on anxiety- and depressive-like behaviors, as well as more recently, on dysbiosis in autism (Mayer et al., 2014). Dysbiosis additionally happens in functional gastrointestinal disorders (FGID), which are strongly connected to mental illnesses and have a disruption of GBA (Mayer et al., 2014). There is evidence in Mayer et al (2014) that both brain-gut and gut-brain dysfunctions exist, with the former predominating in irritable bowel syndrome, IBS in particular (Berrill et al., 2013), and the GBA is disrupted, which results in visceral

hypersensitivity, abnormalities in intestinal motility and secretion, and cellular changes in the entero-endocrine and immune systems. In the opinion of DuPont (2014), multiple lines of evidence suggest that the microbiota may interact with several of these different pathophysiological IBS targets.

As shown by *Lactobacillus reuteri*, which influences gut motility and pain perception by raising their excitability by preventing the opening of calcium-dependent potassium channels, microbiota may also interact with GBA via the regulation of afferent sensory neurons (Kunze et al., 2009). Furthermore, the microbiota may affect the activity of the ENS by releasing chemicals that can function as local neurotransmitters, such as gamma-aminobutyric acid (GABA), serotonin, melatonin, histamine, and acetylcholine, as well as by synthesizing a physiologically active version of catecholamine in the gut lumen (Sobko et al., 2006).

1.6.5 Gut as 'the Second Brain'

The GI tract's neuronal cell lining, which is made up of 100 million neurons, is so vast that it has the moniker "second brain"(Woo, 2021). According to Woo (2021), this network of neurons, sometimes referred to as the ENS, is frequently disregarded and has more nerve cells than the spinal cord or PNS. These are picked up by the nerve, which subsequently transmits information to the brain to control the digestion processes (Woo, 2021). Contrarily, when the vagus nerve is compromised by stress (which prioritizes the muscles and brain), it is less able to respond to inflammation, which is harmful to the gut and gut flora (Edermaniger, 2021). Evidence from a study by Bravo et al. (2011) states that the vagus nerve, which communicates information from the luminal environment to the CNS, is involved in microbial communication with the brain. In actuality, vasectomized mice showed no neurochemical or behavioral consequences, indicating that the vagus is the main modulatory constitutive communication channel between the microbiota and the brain (Edermaniger,

2021). The anxiolytic effect of *Bifidobacterium longum* therapy in a model of chronic colitis linked to anxiety-like behavior was abolished in mice that had undergone vagotomy before the induction of colitis (Bercik et al., 2011). Moreover, Bercik et al. (20211) stated that microbiota could communicate with GBA via a variety of methods, with the regulation of the intestinal barrier likely being the main one, and that this barrier might affect all the underlying systems if it is disturbed. Using measures of plasma cortisol and catecholamine, pre-treatment of animals with a probiotic contents combining *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 restored tight junction barrier integrity and reduced hypothalamic-pituitary-adrenal (HPA) axis and ANS activity (Ait-Belgnaoui et al., 2014).

1.6.6 Link between Gut microbiome and depression

Limbana et al. (2020) claimed that the role of gut flora on mood and mental health is crucial as they may lessen the signs of stress, anxiety, and depression, but they may also exacerbate them. The interplay between the stomach and the brain helps make sense of the mounting evidence that the gut affects both brain health and illness (Limbana et al., 2020). The connection between gastrointestinal and mental health may be explained by inflammation, which is a defining feature of mental disease (Limbana et al., 2020). Limbana et al. (2020) stated that the gut microbiota and vagus nerve are probably both implicated in this. It has been shown that stimulating the vagus nerve reduces stress and inflammation, and some researchers are even speculating that vagus stimulation may be a new kind of drug-free antidepressant (Woo, 2021). Even the probiotic *Lactobacillus rhamnosus*, one of the beneficial gut bacteria, may instruct neurons to produce GABA, a calming neurotransmitter. Additionally, gut microorganisms support neuroplasticity, a process linked to mood (Woo, 2021).

Influence of gut on the nervous system: The ability of the CNS to control gastrointestinal processes such as motility, the release of digestive juices, immunological response, blood flow, and nociception has long been known (Fung et al., 2017). Additionally, the composition and operation of the gut microbiota may be further impacted by brain-gut signaling through the intestinal immune system (Silva et al., 2020). Contrarily, a growing body of research suggests that the metabolites of the gut microbiota have a significant impact on the brain, which may affect the onset of neurological and psychiatric disorders in particular autism, Parkinson's disease, major depressive disorder, and anxiety disorders (Fung et al., 2017).

Biological indicators of depression: The investigation of Radjabzadeh et al. (2022) uncovered that 16 different bacterial species that, to differing degrees, the scientists referred to as "important predictors" of depression symptoms. For instance, the research, which was published in Nature Communications, discovered that those who were sad had lower levels of the bacteria *Eubacterium ventriosum* (Radjabzadeh et al., 2022). It is interesting to note from Radjabzadeh et al. (2022) that this drop has also been seen in microbiome analyses of obesity and traumatic brain injury, both of which are associated with depression, reinforcing the idea that this particular bacterial species may play a role in this mood illness.

The butyrate impact on intestinal microbes and psychological wellness: Edermaniger (2021) claimed when someone consumes plants (fruits, vegetables, seeds, nuts, whole grains, and legumes), their healthy gut flora makes butyrate, an important short-chain fatty acid which not only does keep the stomach content, but the brain does too. How much butyrate is generated by gut bacteria may be determined through a microbiome assessment offered by Atlas Biomed (Edermaniger, 2021). As the primary fuel source for the cells that make up the gut lining, butyrate contributes to the strength and integrity of this barrier (Edermaniger,

2021). Additionally, it was also mentioned by Edermaniger, (2021) that it aids in reducing inflammation, which may be depressing. Recent research even suggests that butyrate could aid in the development of new brain cells (Edermaniger, 2021). However, if there is dysbiosis, the gut bacteria may produce butyrate and other minor nutrients (Edermaniger, 2021).

Microbiota-gut-brain (MGB) axis: Cryan and Dinan (2012) stated that the neurological, endocrine, and immunological systems all play a role in the bilateral interaction that occurs between the gut and the brain. The notion of an MGB axis was developed as a consequence of the crucial function played by the microbiota and the metabolites they produce in gut-brain connectivity (Cryan et al., 2019). As borne out of the altered microbial composition and metabolites in MDD patients by Ghosh et al. (2021), the gut microenvironment's equilibrium gets tampered with, which affects the activity of the gut epithelium and contributes to intestinal barrier collapse and inflammatory responses. Enhanced Th17/Treg disarray, IL-6, IL-1, and tumor necrosis factor-alpha (TNF-alpha) levels, in addition to boosted systemic translocation of gut compounds, microbial cell factors, or even the microbiota via the undermined intestinal barrier, all chip into the pathogenesis of depressive conditions (Kiecolt-Glaser et al., 2018). By modifying gut secretion, immunological responses, elasticity, and permeation, dysfunctional ENS activity resulting from intestinal illness exacerbates the pathogenic alterations driven by depression (Fried et al., 2021). Liu et al. (2023) stated that the vagus nerve, in addition to the ENS, is crucial in the conveyance of microbial signals from the stomach to the nervous system in depressive episodes. As an extension of the brain-gut axis, the HPA axis can be activated by microscopic indications, pathological neurobiological shifts, and moody sentiments, resulting in higher cortisol synthesis and liberation, and excessive amounts of cortisol additionally foster gut pathology by modulating intestinal barrier function and inflammatory responses, leading to the leaky digestive tract, which is a critical aspect of the MGB axis in depression (Młynarska

et al., 2022). Chevalier et al. (2020) mentioned that apart from these networks, numerous signal transduction cascades and metabolic pathways, including the endocannabinoid system, CAMKII-CREB and MAPK signaling, and glycerophospholipid breakdown, are also connected to the MGB-based pathophysiology of melancholy. Furthermore, it has been suggested by L. Liu et al. (2021) that mitochondria may be significant drivers of the connection between depressive disorders and dysbiosis of the microbiota in the intestines. The routes involved in the dual interaction between the stomach and the brain compose a complicated network of mechanisms, and their interactions make it more challenging to comprehend the processes by which the gut microbiota governs depression (L. Liu et al., 2023). The association of MGB with depression is illustrated in the figure below.

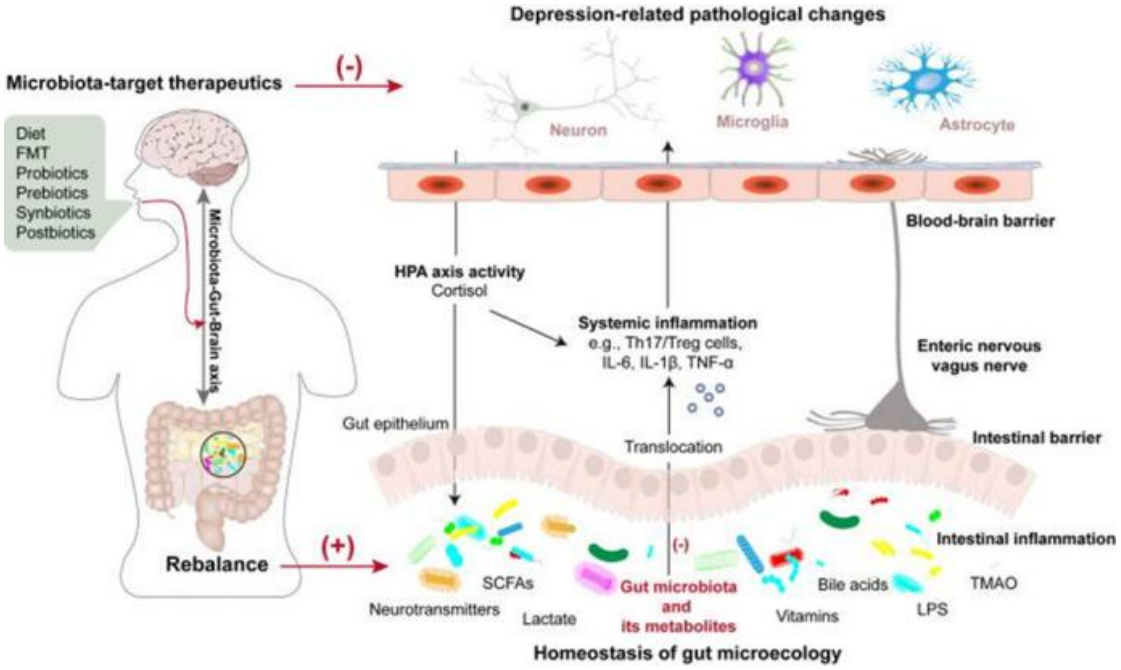

Fig.2. The prospective role of the microbiota-gut-brain axis in the development of depression and treatments that target the microbiome. Fecal microbiota transplantation (FMT), hypothalamic-pituitary-adrenal (HPA), hypomethylating-N-oxide (TMAO), short-chain fatty acids (SCFAs), lipopolysaccharide (LPS), IL-6, IL-1, and TNF-alpha are all terms used in this article. Adopted from (L. Liu et al., 2023).

Chapter 2

Evidence demonstrating the potential link between gut microbes and the occurrence of depression

2.1 Gut-brain communication

Strong evidence provided by Carabotti (2015) demonstrates the importance of gut bacteria in the bidirectional connections between the neurological system and the gut. It interacts with the CNS by modulating the brain's chemical makeup and affecting the neuroendocrine systems involved in stress response, anxiety, and memory (Carabotti, 2015). Additionally, the effects of CNS on microbiota composition are probably caused by a disruption of the typical luminal/mucosal habitat, which can be corrected with the help of probiotics and perhaps even diet (Carabotti, 2015). In the opinion of Carabotti (2015) IBS, now recognized as a microbiome-GBA illness, is one example of this relationship in therapeutic practice for FGID. Unbalanced gut flora can affect anxiety and stress levels by acting in the digestive tract, which is an obscure fact that has effects on mood (Stewart, 2020). They can help us become more resilient to stressful situations, but if the ecosystem is out of balance (dysbiosis), their actions could be detrimental to our mental health. Stewart (2020) states the multiple ways that the brain and gut microbes interplay during challenging circumstances:

The gut-brain highway: Stewart (2020) states one can breathe, swallow, and digest automatically under the autonomic nervous system, which is largely controlled by the vagus nerve. This nerve is made up of fibers that travel from the brainstem to our digestive tracts, where they are encased in the epithelium, the lining of the aforementioned tracts (Stewart, 2020). The brain and the gut can interact with each other owing to this highway (Stewart, 2020). Furthermore, it is mentioned by Stewart (2020) that gut lining cells are linked to the

vagus nerve fibers as they employ these cells to gather data on gut and microbiome activity and convey this data to the brain so that it can make critical digestion-related decisions. The vagus nerve thus plays a role in food intake, secretions of digestive chemicals, and muscle movements that drive food through the gastrointestinal tract (Stewart, 2020). Additionally, it can stop the permeability of the gut lining and instruct the brain to stop releasing anti-inflammatory compounds in response to intestinal inflammation (Stewart, 2020). As claimed by Stewart (2020) the vagus nerve can detect metabolites in particular butyrate, which is produced when gut bacteria break down food particles then this nerve sends all this data to the brain, influencing digestive functions. Yet, stress causes the vagus nerve to cease functioning, which prevents it from carrying out these crucial functions (Stewart, 2020). Moreover, Stewart (2020) asserted that stress can prevent the vagus nerve from responding, which prevents it from releasing anti-inflammatory chemicals that reduce inflammation. Stress and inflammation can affect the environment on account of gut microbes being susceptible and the vagus nerve is also unable to regulate the permeability of the gut lining when it is blocked by stress (Stewart, 2020). Stewart (2020) further stated that the blood-brain barrier, which is meant to shield the brain from pathogens and illnesses, can be breached by some bacteria, metabolites, and toxins if the gut lining remains permeable. In the words of expert Miguel Toribio-Mateas, stress can alter both the abundance and diversity of microorganisms (Stewart, 2020). It is mentioned by Stewart (2020) that the hypothalamic-pituitary-adrenal (HPA) axis, a mechanism of gut-brain communication, may be compromised, which could affect mood. Although there is bidirectional communication between the alimentary tract and the brain, messages coming from the gut to the brain are stronger than those coming from the brain down (Stewart, 2020).

Probiotic gut bacteria: Probiotics are composed of living, healthy bacteria and/or yeast that exist abundantly in the human digestive tract (Professional, 2023). Ansari et al. (2023)

affirmed that the colon contains species of *Bifidobacterium*, *Lactobacillus* (lactic acid bacteria), and *Lactococcus* that have a good impact on overall health, including anxiety and stress. This is because probiotic bacteria contribute to a healthy gut microbiome overall well-being (Ansari et al., 2023). They also create other types of advantageous bacteria in addition to crucial short-chain fatty acids and other nutrients for the body (Ansari et al., 2023). As an illustration, *Bifidobacteria* create acetate, an SCFA that *Eubacterium* uses to form butyrate (Ansari et al., 2023). Additionally, SCFAs aid in intestinal acidification and optimal pH. It is advantageous on account of the acidity that prevents diseases from colonizing while simultaneously creating the ideal conditions for helpful bacteria to flourish (Carabotti, 2015). In turn, this aids in reducing inflammation and maintaining the strength of the gut lining (Carabotti, 2015). Investigations in the field of psychobiotics from Carabotti (2015), which studies the impact of probiotic microorganisms on our psychological well-being, have also revealed that certain *Lactobacillus* species help us become more resilient to stress and lessen its negative effects on our memory, cognition, and anxiety. Among them are *L. rhamnosus, L. rhamnosus, L. rhamnosus, L. plantarum*, and *L. acidophilus* (Carabotti, 2015).

2.2 Dysbiosis of the gut microbiota and depression

Dysbiosis of the gut microbiota can result from a negative lifestyle brought on by excessive and persistent stress, the spread of infection, or additional factors (Chang et al., 2022). As stated by Chang et al. (2022) the brain-gut-microbiota axis may govern abnormal bodily instances in both directions via neurological, immunological, or chemical signals, which can lead to depression. Growing numbers of clinical and preclinical studies established by Liu et al. (2023) that dysbiosis, or changes in the structure and functioning of the bacteria in the gut, interferes with the development and course of depression by modifying the gut-brain axis. The figure below demonstrates the correlation between dysbiosis in gut and depression.

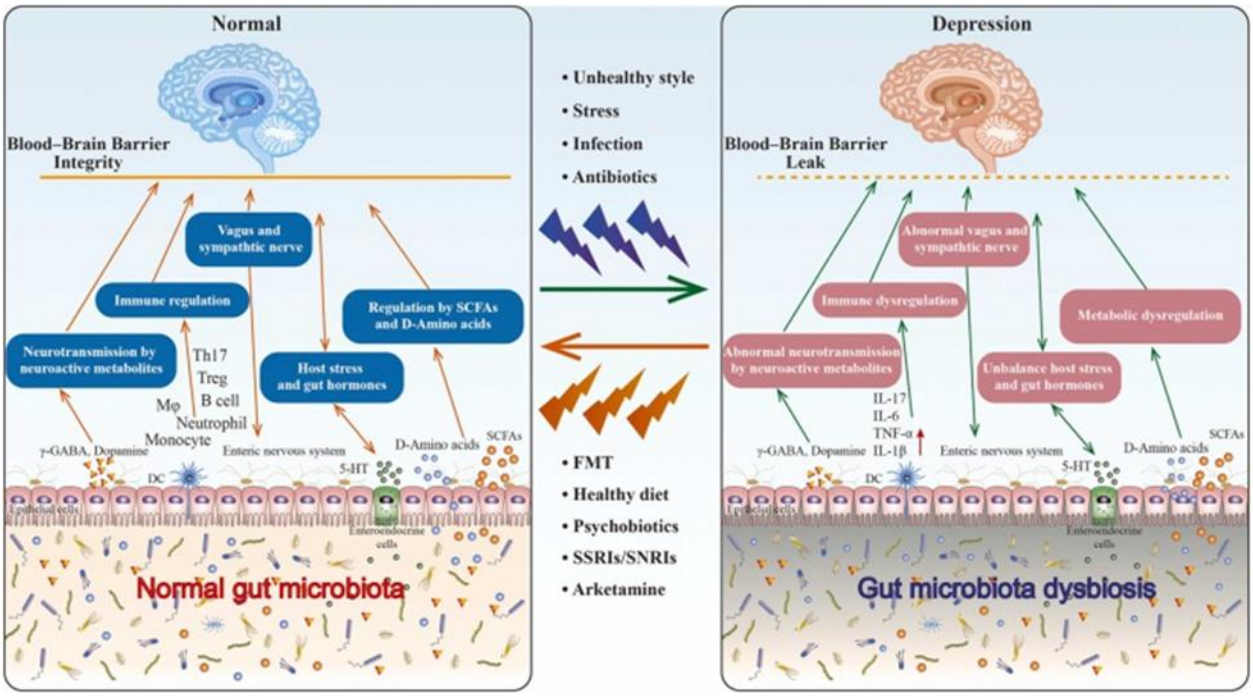

Fig.3. The connections between depressive disorders and the microbiome and CNS. Extracted from (Chang et al., 2022).

By juxtaposing alterations in the gut microbial composition of MDD patients to healthy persons, most notably in terms of the diversity of microbial species and the proportionality of particular bacterial taxa, accumulating studies have demonstrated a connection between dysbiosis and depression (Nikolova et al., 2021). Simpson et al. (2021) stated that *Firmicutes, Actinobacteria, and Bacteroidetes* are the three phyla that are most frequently impacted by despair; in particular, MDD patients have an increased *Bacteroidetes/Firmicutes* ratio, which is characterized by an enrichment of the species Bacteroides and a depletion of the genera *Blautia, Faecalibacterium,* and *Coprococcus*. Fecal microbiota from MDD patients has been grafted into mice to cause depressive-like behaviors, therefore showing that microbial dysbiosis can lead to the onset of MDD or contribute to the disorder (Kelly et al., 2016). There is confirmation of a pathological spiral stated by Chidambaram et al. (2022) that dysbiosis is both a source of and an aggravator of depression-related pathological alterations. Consequently, whereas early-stage changes in the microbiome may have contributed to the

development of MDD, ongoing pathological abnormalities in MDD also contribute to dysbiosis by changing the gut environment (L. Liu et al., 2023). The illustration below shows the alterations in the gut microbial diversity because of depression.

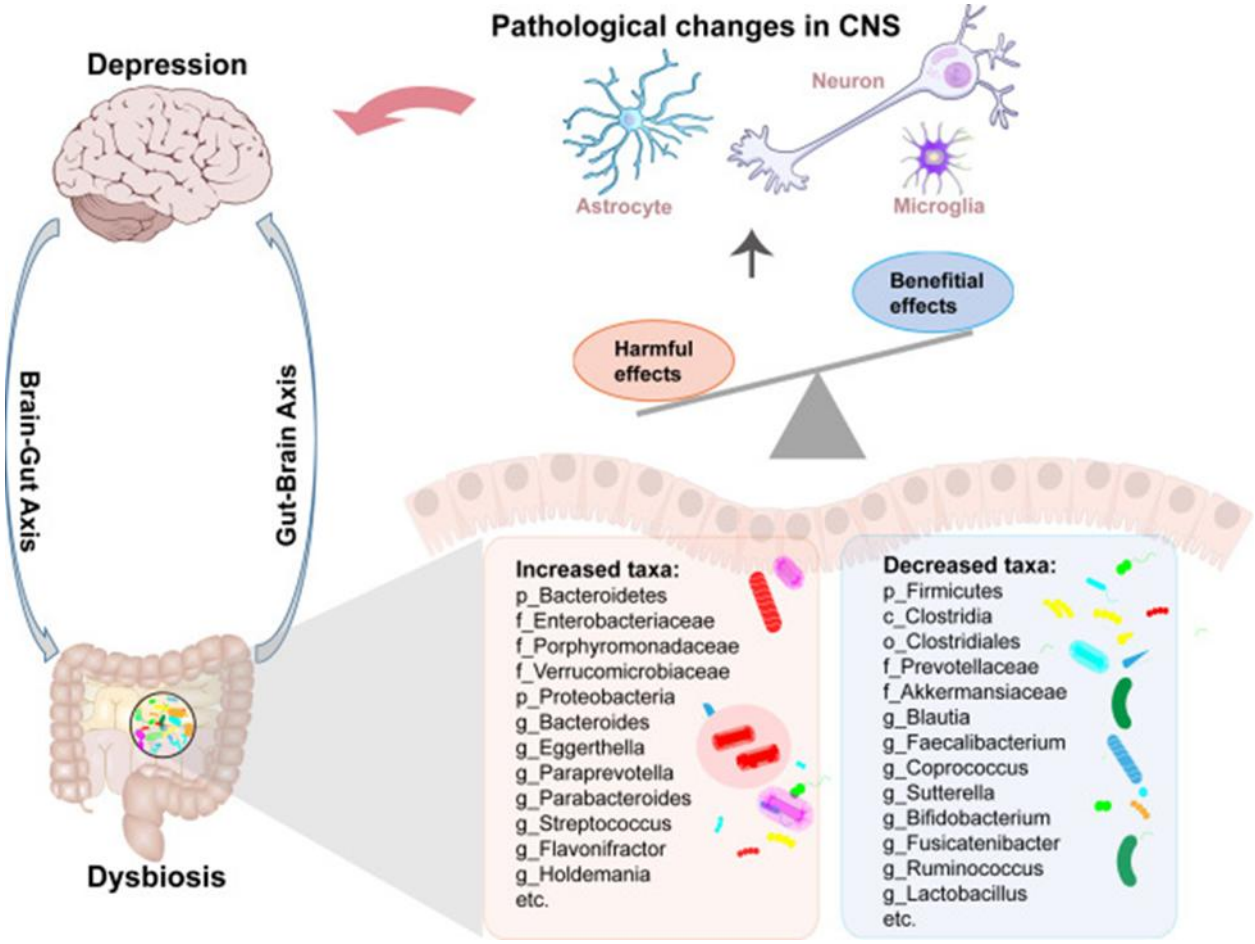

Fig.4. Dysbiosis and central pathological alterations associated with the onset of a depressive disorder are shown. Adopted from Liu et al. (2023).

Nevertheless, in the framework of the intricate gut microbial community, a few specific pathobionts presumably act constructively in collaboration to produce grief instead of serving solely as solitary pathogenic microbes (L. Liu et al., 2023). In accord with Ludington (2022), the processes behind the microbiome-host interactions that lead to depression may be made easier by knowing these higher-order communications, which yield novel effector molecules.

2.3 Serotonin and GABA

Serotonin and GABA are key compounds for mental wellness that are produced and regulated by gut microbes (Salters-Pedneault, 2023). Salters-Pedneault (2023) claims that serotonin plays a role in mood, happiness, and anxiety regulation when our bodies have enough of it. Dolefulness, however, has been linked to low serotonin levels (Salters-Pedneault, 2023). In the opinion of Professional (2022), GABA is a comparatively unknown neurotransmitter, but studies show that it contributes to mood regulation and enhancement. Serotonin makes it easier for the brain and nervous system cells to communicate (Professional, 2023).

2.4 The association between the gut flora, GBA, and serotonin metabolism

According to Stasi et al. (2019), changes in the gut flora may influence serotonin signaling. The first sign related to the changes in commensal bacterial makeup and intestinal transit time brought on by antibiotic treatment (Stasi et al., 2019). The second suggestion asserted by Stasi et al. (2019) focused on variations in serotonin levels linked to particular microorganisms. The third signal concerned the connection between decreased serotonin transporter expression and a change in the gut's microbiota from one of homeostasis to one of inflammation (Stasi et al., 2019). As cited by Salters-Pedneault (2023), serotonin regulates visceral pain, secretion, and the onset of the peristaltic reflex, whereas its levels are also found to be abnormal in a wide range of psychiatric diseases. A neuro-endocrine-immune stimulus may cause dysregulation in the CNS, dysregulation at the peripheral level (intestine), or a combination of both (brain-gut axis) in various gastrointestinal functional disorders (Stasi et al., 2019).

Chapter 3

Evidences from pre-clinical, observational and interventional studies

Alli et al. (2022) executed a systematic evaluation with 24 case-control studies (n = 2817) and 19 interventional experiments (n = 1119) as subjects of study. In patients with MDD versus those with Healthy Controls (HC), researchers evaluated alpha, beta, and taxonomic abundance changes (Alli et al., 2022).

Alli et al. (2022) suggested that the gut-brain axis plays an integral role in the emergence of despair. The GBA is a neuroimmune and neuroendocrine-driven reciprocal system that communicates between the cognitive system along with the intestinal tract (Hooper et al., 2003). In accord with Wikoff et al. (2009), SCFAs, secondary bile acids, GABA neurotransmitters, and tryptophan metabolites, all of which are produced by the microbes, are some of the molecules that mediate it. Gut-brain linkages are disrupted and implicated in alterations in blood-brain barrier transparency and neuroinflammation through imbalance, or a disturbance of the microbial balance (Rutsch et al., 2020).

3.1 Pre-clinical trials

Chang et al. (2022) affirmed that stress contributes to the pathophysiology of depressive symptoms as well as that adaptative alterations in several circuits, including BDNF, pro-inflammatory cytokines, and the spleen, drive resilience. Investigations have revealed that certain rodents are resistant to learned helplessness (LH) and chronic social defeat stress (CSDS), and the researchers found increased *Bifidobacterium* counts in CSDS-resilient mice than in control and CSDS-vulnerable organisms (Chang et al., 2022). Additionally, as compared to vehicle treatment by Yang et al. (2017), oral administration of *Bifidobacterium* substantially increased the number of mice resistant to CSDS, indicating that *Bifidobacterium*

provides robustness to CSDS (Chang et al., 2022). In addition, K. Zhang et al. (2019) asserted that LH-susceptible rats had drastically higher corresponding distributions of the genera *Lactobacillus, Clostridium cluster III,* and *Anaerofustis* than control and LH-resilient rats, as well as fewer quantities of acetic and propionic acids in their feces than control and LH resilient rodents did. It is fascinating to note that in mice, resistance to CSDS is correlated with antibiotic-induced microbiota decline (Wang et al., 2020). Likewise Qu et al. (2020) stated that, betaine supplementation has been proven to have anti-inflammatory effects that help mice with CSDS maintain their resistance to anhedonia. In tandem, these data provide evidence that the brain, gut, and microbiome axis contribute to both vulnerability and resistance to stress (Hashimoto, 2020). As stated by Wu et al. (2020), the gut microbiota-related SCFAs along with additional metabolites such as alanine, isoleucine, L-threonine, serine, and tyrosine are abnormally high in stress-induced depression-like demeanors in rodents and these metabolites may be linked to depressive-like phenotypes and altered levels of 5-HT in the cerebrum. In contrast to controls, rodents with FMT of the "melancholic microbiome" had depressive-like traits (Knudsen et al., 2021). On the contrary, it has been demonstrated by Van De Wouw et al. (2018) that therapy with a combination of SCFAs, including acetate, butyrate, and propionate, reduces stress-induced depressive-like behaviors in mice.

3.2 Observational Studies

This study examined and compared the gut microbial community of patients with MDD and HC individuals, relying on data from 24 observational studies (Alli et al., 2022).

References	Alpha Diversity	Beta Diversity
Kelly 2016 (Kelly et al., 2016)	Decrease	No change
Huang 2018 (Huang et al., 2018)	Decrease	No change
Rong 2019 (Han et al., 2019)	Decrease	ND
Liu 2020 (Liu et al., 2020)	Decrease	No change
Rhee 2020 (Rhee et al., 2020)	Increase	No change

Table 4: Following the findings of 24 study findings, the prevalence of microbial taxa in patients having MDD in comparison to HCs is outlined. Only five of the patient's taxonomic counts have either decreased or increased in 24 trials. The remaining ones remained not declared (ND). A handful of the trials revealed notable modifications, but they did not state whether the taxa ascended or fell.

A synopsis of the group of microbes that were altered during the trial is given below:

Elevated group of microbes	Demoted group of microbes
Bifidobacteriaceae	*Bacteroides*
Streptococcaceae	*Sutterellaceae*
Eggerthella	*Coprococcus*
Streptococcus	*Faecalibacterium*

Table 5: A compilation of the variations in taxonomic abundance in patients with MDD is provided. Patients with MDD had higher levels of the following species: the genera Eggerthella (six trials), Streptococcus (five trials), and the families Bifidobacteriaceae and Streptococcaceae (four trials). On the contrary, there had been a decline in the number of studies in the phylum Bacteroidetes (four trials), family Sutterellaceae (four trials), genus Coprococcus (six trials), and genus Faecalibacterium (seven trials).

3.3 Interventional trials

Microbiota research was conducted as part of five of the interventional trials (Chahwan et al., 2019). In the opinion of Tian et al. (2022), and Alli et al. (2022) the findings from four studies using taxa abundance evaluations indicated that probiotic-treated patients had higher proportions of *Ruminococcus gauvreauii*, *Coprococcus 3*, *Desulfovibrio, Faecalibacterium, Bifidobacterium, Adlercreutzia, Megasphaera, and Veillonella* in contrast to untreated

patients and lower proportions of *Rikenellaceae_RC9_gut_group, Sutterella,* and *Oscillibacter*.

In the above investigations, there was a substantial difference in alpha diversity between patients with MDD and HC. Patients with psychiatric illnesses were considered to have decreased alpha diversity. These results support the idea that MDD involves a dysbiotic condition since they are in line with research on patients who has MDD as well as research on mental illnesses more generally where alterations in alpha diversity have been identified. Concerning putative processes, two studies hypothesized that alterations in depressive symptoms might be brought on by an alteration in the composition of GMB as a result of a dietary supplement (Alli et al., 2022). In patients who received *Bifidobacterium breve CCFM1025* as a supplement, there was a rise in the effluence of *Bifidobacterium* in the fecal microbiota over four weeks (Reininghaus et al., 2020). *Bifidobacterium breve CCFM1025* and OMNi-BiOTiC® Stress Repair medication throughout four weeks also increased *Coprococcus* (Reininghaus et al., 2020) and *Faecalibacterium* (Tian et al., 2022) genera, which are often low in MDD (Alli et al., 2022). These results obtained by Alli et al. (2022) imply that augmentation may affect the pharmacokinetics and pharmacodynamics of GMB alongside depressive symptoms in depressed patients.

Chapter 4

Limitations and knowledge gaps in the field of GBA

Limitation

At first glance, this review focused on the potential of the gut microbiota for correlating to depressive disorders. Consequently, the paper did not devote ample time to discussing the pathogenic pathways involving the gut-brain implicated in the control of depression by the gut microbiota or how these gut microorganisms aid in alleviating depression as sufficient information is not available to elucidate the pathogenic mechanisms underlying microbiome-induced depression. Uncertainty exists regarding the specific processes that lie behind the brain-gut-microbiota axis' contribution to depression (L. Liu et al., 2023). Future relevant systematic studies are needed to more accurately assess the effects of gut flora on antidepressant medications and the effectiveness of gut microbiota-targeted intervention techniques for depression. Establishing therapies for depressive disorders that target the intestinal microbial community is nevertheless fraught with difficulties, but researchers are hopeful that new developments in technology and strategy may help to overcome these impediments.

Knowledge gaps

Despite particular gut microbial alterations not consistently found within research, dysbiosis is linked to depression. The overall composition of the gut microbiota in two healthy people is likely to differ significantly since the gut microbiota can be altered easily by external influences, in particular the food source. Future research ought to clarify how different complicating variables affect gut microbiota. Large-scale prospective studies are likewise vital to pinpoint the distinctive microbe modifications of depression that alter concurrently

with the indications of depression and detect the pathogenic and beneficial varieties that trigger despondency and their cause-effect relationships. Additionally, it is required to flesh out the underlying gut-brain mechanisms involved in the pathogenesis of clinical depression. Meanwhile, while investigating the function of certain bacterial strains and creating gut microbiota-target therapies, there are a variety of bacteria-bacteria and bacteria-metabolite interactions that need to be taken into attention. Future investigation is required to better understand the inter-linkage between the gut flora and the host as well as the potential effects of therapies aimed at the microbiome on the host.

Chapter 5

Future Implications

To identify the causative links between dysbiosis, depression, and treatment, more prospective studies are needed to examine the interaction between the onset of depression and dysbiosis, as well as drug-microbiota interactions. It is speculated that the relationship between the brain, gut, and microbiome could lead to novel approaches to treating despair. Innovative therapy strategies for promoting mental health will be made accessible by a greater comprehension of the brain, gut, and microbiome axis in depression. Delineating the pathogenic process in the MGB axis and locating the main stressors could be a game changer indeed. Additional study is required to identify the pathogenic and beneficial challenges triggering depression, identify the specific roles played by these strains, and uncover the underlying mechanisms involved in the GBA. Such research should make use of the most advanced high-throughput sequencing (HTS), multi-omics, and microbe cultivation techniques. According to (L. Liu et al., 2023), the advancement of microbiota-based therapy options for depression depends on the establishment of new technologies, such as isotope tracing, modified strains, and CRISPR-edited strains as this will lay the groundwork to encourage the use of personalized medicine based on microbiota to combat depression which could be the upcoming frontier in microbiome exploration; however further discussions on the mentioned strains were not elaborated.

Chapter 6

Conclusion

The goal of this review article is to ascertain how the gut microbiome links mental health and depression. The gut-brain axis is an important factor to take into account while managing a variety of mental disorders and psychiatric illnesses. The structure, characteristics, or abundance of gut microbes that control specific behaviors throughout the range of mental health and illness require further laboratory research. Researchers are still a long way from understanding how these magnificent gut microorganisms affect our ability to process information. However, if the undiscovered areas are completely comprehended, it will be able to overcome obstacles in the treatment of many untreatable psychiatric conditions. However, more comprehensive and extensive double-blind randomized-controlled trials are required, taking into account aggravating elements such as symptom intensity, age, nutrition, and medication use. Before these forms of treatment move to the implementation stage as treatments for depression, important concerns in particular the species provided, dosage, and time of therapy still need to be answered.

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