universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master 's Thesis

„Gut dysbiosis and its relationship with the brain and possible treatment – a literature review "

verfasst von / submitted by

Amr Negm

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Magister pharmaciae (Mag.pharm.)

Wien, 2022 / Vienna, 2022

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	UA 066 605
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Masterstudium Pharmazie
Betreut von / Supervisor:	ao. Univ.-Prof. Mag. Dr. Christian Studenik

Acknowledgement

Firstly, all thanks to god, the most gracious and merciful, for blessing me with the strength to accomplish my master's thesis.

I warmly thank Ao. Univ.-Prof. Mag. Dr. Christian Studenik, a professor in the pharmaceutical sciences department at the University of Vienna in Austria, gave me the chance to do my master’s thesis under his supervision.

Dr. Mohamed Aufy, a senior lecturer in the pharmaceutical sciences department at the University of Vienna, deserve my acknowledgement and warm thanks for his assistance and ongoing conversation in presenting new issues on this topic and covering it thoroughly. When we met, he was always encouraged at every appointment.

Special thanks also go to my professor. Haytham O. Twafik, associate professor in the department of pharmaceutical chemistry at Tanta University in Egypt, for his encouragement and support as a teaching assistant.

My heartfelt gratitude goes to my colleagues at the Engel Pharmacy in Traiskrichen, Austria, for their emotional support.

My sincere thanks to my friends from Egypt or here in Austria.

Finally, I dedicate my MSc thesis to my parents, my sister, and my brother for their support throughout the challenging period and for dealing with my mood swings during my master’s studies.

Abstract

The impact of the gut-brain axis on our biological functions is enormous. Dysbiosis and microbiota imbalance cause changes in the intestinal immune system and neurological system dysfunction. Dysbiosis is exacerbated by a changed gut environment, which contributes to the development of various conditions, including neuropsychiatric diseases, chronic diseases, autoimmune diseases, and respiratory diseases. The gut-brain axis impacts not just the aetiology of many diseases but also the efficacy of drugs in treating these disorders. The use of bacterial preparations are not new, but they have existed in the past, such as the usage of yellow soup in ancient Chinese culture to treat food poisoning. Nowadays, the man may find a variety of medicinal preparations on the market that include probiotics or prebiotics to cure various disorders. Anti-diarrhea medications, for example, contain a variety of helpful bacterial strains as well as nutrients. Much research has focused on this bidirectional connection between the gut and the brain for many years. A comprehensive study of this topic is required to understand the similarities and differences of gut bacteria that play a significant role in the pathogenesis of various disorders and to try to exploit them in the treatment of numerous illnesses, providing many ideas for promising methods in the treatment of these diseases.

Kurzfassung

Der Einfluss der Darm-Hirn-Achse auf unsere biologischen Funktionen ist enorm. Dysbiose und Mikrobiota-Ungleichgewicht verursachen Veränderungen im intestinalen Immunsystem und Funktionsstörungen des neurologischen Systems. Dysbiose wird durch eine veränderte Darmumgebung verschlimmert, die zur Entwicklung verschiedener Erkrankungen beiträgt, darunter neuropsychiatrische Erkrankungen, chronische Erkrankungen, Autoimmunerkrankungen und Atemwegserkrankungen. Die Darm-Hirn-Achse beeinflusst nicht nur die Ätiologie vieler Krankheiten, sondern auch die Wirksamkeit von Arzneimitteln bei der Behandlung dieser Störungen. Die Verwendung von bakteriellen Präparaten ist nicht neu, sondern sie hat in der Vergangenheit existiert, wie die Verwendung von gelber Suppe in der alten chinesischen Kultur zur Behandlung von Lebensmittelvergiftungen. Heutzutage kann der Mann eine Vielzahl von medizinischen Präparaten auf dem Markt finden, die Probiotika oder Präbiotika enthalten, um verschiedene Erkrankungen zu heilen. Medikamente gegen Durchfall enthalten beispielsweise eine Vielzahl hilfreicher Bakterienstämme sowie Nährstoffe. Auf diese bidirektionale Verbindung zwischen Darm und Gehirn konzentriert sich seit vielen Jahren viel Forschung. Um die Ähnlichkeiten und Unterschiede von Darmbakterien zu verstehen, die eine bedeutende Rolle bei der Pathogenese verschiedener Erkrankungen spielen, und um zu versuchen, sie für die Behandlung zahlreicher Krankheiten zu nutzen, ist eine umfassende Untersuchung dieses Themas erforderlich, um viele Ideen für vielversprechende Behandlungsmethoden zu liefern dieser Krankheiten.

Table of Contents

1. Introduction

The nature of communication between the gut and the central nervous system, how it influences our physiological and psychological functions, and how it relates to various disorders have been the focus of research over the last ten years. Numerous studies demonstrate how the gut and brain interact. As is well known, the neurological system regulates how the gastrointestinal tract works. On the other hand, the intestinal microbiomes metabolize the nutrient to form certain metabolites that take part in neurotransmitter synthesis, obstruct the hormone-building pathway, or impact the intestinal immune system. The impact of the gut on the brain is reflected in this effect by these bacteria, whether microbiomes or dysbiosis. The effects can affect the gut mucosa directly or indirectly by altering the brain's synthase route, particularly in the hypothalamic-pituitary-adrenal (HPA) axis [1], [2].

When dysbiosis interferes with the connection between the gut and the brain, the gut runs this bidirectional way in a stable way. According to research, dysbiosis substantially impacts the pathophysiology of various psychiatric and neurological disorders. With the aid of identifying the gut bacteria, the cause of Alzheimer's disease was better understood [3]. The pathophysiology of irritable bowel disorder remained unclear. Until researchers looked at how gut microbiomes contributed to this physiological instability, this disorder's nature could be clarified [4]. Although chronic conditions like diabetes and heart disease are now effectively addressed. The utilization of the gut microbiota in treating and developing chronic diseases was also studied [5], [6]. Current research focuses on elucidating neuropsychiatric illness and other illnesses such as stroke-related inflammation and potential cancer treatment targets [7], [8]. Some studies are interesting in examining the involvement of the gut microbiome in autoimmune illnesses like multiple sclerosis because it modulates the immune system in the gut [9]. Also, attempts to find the reported information concerning the function of dysbiosis in conditions like autism and attention deficit hyperactivity disorder (ADHD) [10], [11]. This research attempted to determine whether the gut-brain axis may have played a part in Covid-19's viral infection [12].

We can make potential medical discoveries in the same way that fecal microbiome transplantation was used to treat the *Clostridium difficile* infection by thoroughly studying the causes of each disease and how the brain-gut axis functions [13]. The best use of nutrients, known as prebiotics, to improve the gut environment and encourage the growth of the gut bacteria in the gut, so they can overcome the harmful bacteria, or use specific bacteria spices,

known as probiotics, or use some bacteria, which can combat itself the dysbiosis and produce the beneficial metabolites. The term "symbiotic" refers to these bacteria that have both choices [14]. The interaction between the host and intestinal microbiota provides a wealth of helpful information that can be used to develop new treatment strategies, whether they involve antibiotics or other novel therapeutic ideas [4], [15].

In this review, we will discuss the nature of the gut-brain axis and its role in several disorders, including neuropsychiatric disorders, autoimmune diseases, chronic diseases, and respiratory diseases. Additionally, prospective therapies for various disorders, as well as certain critical therapy techniques that are applicable today or in the future, will be discussed.

2. A description of the Gut-brain axis

Every system impacts every other system, whether directly or indirectly. The CNS regulates the GIT movement, stomach acid secretion, mucus production, ad secretion, and the immune defense of the Intestine and Stomach because the Gut immune cells act as a protective barrier against bacteria and harmful foreign bodies by fighting them or preventing their absorption with the help of macrophages and mast cells either directly or indirectly by enhancing their activity [1].

The enterochromaffin cells, a crucial component of the gut lumen, can secrete serotonin and signaling peptides (such as corticotropin-releasing hormone) in response to various physiological and pathological luminal stimuli, such as a bacterial toxin, after being stimulated by the vagal system. The expression of receptors such as the serotonin receptor, the pituitary adenylates cyclase-activating peptide receptor, the cholinergic receptor, the corticotropin-releasing hormone receptor, and the aminobutyric acid receptor is another function of the enterochromaffin cells [1], [2].

The foundation of the interaction between the gut and brain is gut dysbiosis. They take part in digestion, which produces metabolites that regulate the immune system, such as short-chain fatty acids (SCFAs) and chemotactic peptides. These metabolites can pass the blood-brain barrier, contribute to neurochemical development, and maintain brain tissue homeostasis when they enter the circulation and reach the brain [1], [2].

The metabolism of tryptophan, which plays a part in controlling brain function, is aided by SCFAs. Changes in the regulation of receptors caused by microbiota in the gut lumen directly impact the GIT motility, gastric secretion, and the response of the gut immune system. As an

illustration, the GIT movement is enhanced by *Bifidobacterium bifidum* and *Lactobacillus acidophilus* while being inhibited by *Escherichia* species [1], [2], [16].

Neurochemicals are secreted by the gut flora and interact with lumen receptors directly to exert their physiological effects. These gut bacteria can affect how the epithelium reacts to biopeptides or tripeptides, such as N-formyl methionyl-leucyl-phenylamine, or Toll-like receptor signaling [1], [16].

Gut immunity depends on SCFAs, tryptophan catabolites, and their interactions with the aryl hydrocarbon receptor (AhR) [2]. To protect against dangerous bacteria, this response activates inflammatory and immunological mediators. For instance, *Propionibacterium freudenreichii* ET-3 produces 1,4-dihydroxy-2-naphthoic acid (DHNA), a vitamin B12 precursor that promotes the production of antimicrobial proteins and prevents the colitis that is caused by the DSS synthesis in mice [2]. Inflammatory or stress-related factors stimulate the hypothalamic-pituitary-adrenal (HPA) axis. Corticotrophin Releasing Factor (CRF), secreted by the hypothalamus and circulated through the bloodstream to the pituitary gland, causes the latter to create adrenocorticotrophic hormone (ACTH). The adrenal cortex is influenced by this hormone, which also causes the adrenal glands to create corticosteroids like cortisol. In the gut, cortisol reduces inflammation [17].

Disturbances in the gut microbiome are caused by pathogens and changes in lifestyle or environmental variables. A healthy mouth cavity is home to numerous microbiomes, including *Streptococci* and *Actinomycete*. Many diseases will manifest when the physiological environment changes, such as periodontal diseases combined with *Firmicutes*, *Proteobacteria*, *Spirochaetes*, and *Bacteroidetes*, referred to as Dysbiosis. There is a link between periodontitis and other diseases such as cardiovascular conditions, obesity, respiratory infections, risks during pregnancy, rheumatoid arthritis, and diabetes mellitus [18].

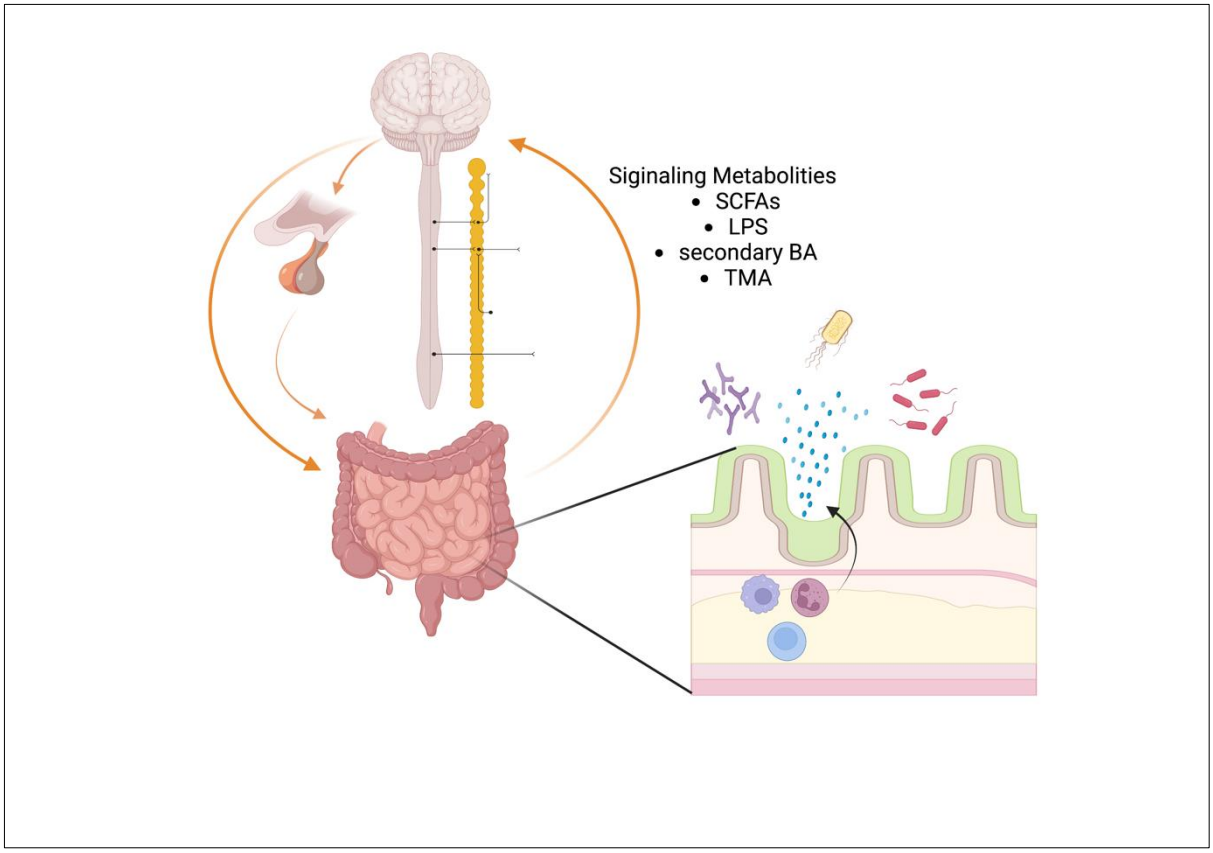

Figure 1. Schematic representation of the Gut- Brain axis with short description:
The CNS and GIT communicate with each other in both directions. The sympathetic and parasympathetic nervous systems actively regulate gastrointestinal tract processes and modulate intestinal immunity. Any change in the environment of the gut immune cells produces a change in how they behave, much as stress changes the permeability of the intestinal portion and increases interferon production. Some common and pathological luminal stimuli, such as bacterial toxins, cause the vagal system to activate enterochromaffin cells in the stomach and secrete serotonin and signaling peptides. Short-chain fatty acids (SCFAs) are involved in digestion and provide neurochemicals and immune-regulatory metabolites. They can affect the CNS when they are released into circulation and reach the CNS, influencing the formation of neurochemicals. They have an immediate effect by interacting with the nervous system's receptors in the gut. Microbiota also influence tryptophan metabolism, which influences how effectively the brain operates. Inflammatory mediators or stress stimulate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in an increase in cortisol release that affects the stomach cavity directly. Toll-like receptor (TLR) signaling can influence the epithelium. LPS, an endotoxin produced by gram-negative bacteria, may also bind to TLRs. Signaling metabolites influence the pathogenesis of various diseases [1], [16], [17].

3. Development of Gut microbiome through life

During vaginal delivery, the newborn acquires its microbiome through interaction with *lactobacillus* and *prevotella* from the mother's vagina and feces. The medical staff, the hospital, and the mother's maternal skin become the microbiome of the babies delivered via Caesarean section. *Proteobacteria* and *Firmicutes* were seen to proliferate within the first few days following delivery, whereas *Actinobacteria* was discovered in the faces of newborns delivered via Caesarean section five days after delivery. Babies born via c-section have fewer complex microbiomes in their guts, fewer species like *Bifidobacterium* and *Bacteroides*, and *Clostridium sensustricto* and *Clostridium difficile*. While it is reported that there is a link between the risk of immunological illnesses such as Asthma, allergy, and type 1 diabetes with the usage of cesarean section, the benefit of the microbiome during vaginal delivery gives the natural birth advantage over C-section delivery [19].

Because preterm neonates require parenteral nourishment, an extended hospital stay, and artificial respiration, microbiome development has been shown to differ between premature and full-term neonates in numerous studies. It has been noted that premature neonates have a different microbiome because anaerobic microorganisms like *Bifidobacterium* and *Bacteroides* take longer to grow. The feces of premature infants included a significant amount of *Enterobacteriaceae, Enterococcus*, and other harmful microbes. Because it raises the risk of necrotizing enterocolitis and species-specific immune responses, this apparent variation in gut microbiome in preterm neonates alters immune response [19].

Breastfeeding is a crucial element in the formation of the microbiota. A combination of nutrients, probiotics, and antibiotics is given during breastfeeding. Breastfeeding gives newborns IgAs, which help to control the immune system. Breast milk contains human milk oligosaccharides, which can control how bacteria grow and evolve. Contrarily, formula-fed children receive various amounts of vitamins, bacteria, and carbs, creating a distinct microbial ecosystem in the gut. According to reports, formula-fed babies' stool contains different bacteria like *Staphylococci*, *Bacteroides*, *Clostridia*, *Enterococci*, *Enterobacteria*, and the genus *Atopobium*, whereas breastfeeding babies' stool contains a high concentration of *Bifidobacteria* and *lactobacilli* and low levels of pathogens [19].

The habitat of the neonate's gut flora is influenced by the mother's body mass index and weight increase throughout pregnancy. It was revealed that overweight mothers had higher concentrations of *Bacteroides* and *Staphylococcus* in their feces, whereas mothers who are not

overweight have higher concentrations of *Bifidobacteria* [18]. The gut flora varies over time because of dietary changes and social changes. It has been demonstrated that the gut flora of one person growing up in an Italian town and another growing up in an African hamlet differ significantly [19].

4. Sex difference in Gut-Brain axis

The human brain differs between men and women. This distinction is based on anatomical structure, activity, molecular profile, and epigenetic modification. Some differences exist at birth, while others emerge during puberty and adulthood. Male brain volume is greater than female brain volume; however, female brain cortical thickness is greater. Males have more remarkable white matter than females, while females have more remarkable grey matter. Estrogen has a pro-inflammatory effect on the immune system, whereas testosterone has an anti-inflammatory effect. Postmenopausal estrogen therapy improved women's neuronal plasticity and congenital function [20].

In both male and female stool samples, there is a higher abundance of *Ruminococcaceae*, *Faecalibacterium*, and *Alistipes*, as well as a lower abundance of *Bacteroides* and a lack of *Prevotella*. On the other hand, male samples had a higher abundance of *Prevotella* and a lower abundance of *Bacteroides*. The greater diversity of *Akkermansia* protects women from physiological and psychological insults. Estradiol levels are thought to favor *Gammaprotebacteria* and *Proteobacteria*, which produce Lipopolysaccharide while negatively affecting *Prevottellaceae*. The increased production of LPS by *Proteobacteria* and the decreased production of SFAs by *Prevotellaceae* increases the risk of mental disorder during the pubertal phase. Oral contraceptive therapy influences Gut microbiomes and increases intestinal permeability, which increases the risk of intestinal inflammatory diseases [20].

Because they influence the expression of estrogen and androgen receptors, the gut microbiota can modulate the effect of hormones and steroids. The sterobiome and estronolme are in charge of steroid or estrogen metabolism. The gut microbiota can convert inactive estrogen from its conjugated form to the active unconjugated form. Ketosteroid reductases are enzymes produced by *Actinobacteria, Proteobacteria*, and *Firmicutes* that convert testosterone to androstenedione and estradiol to oestrone. *Streptococcus* and *Bacillus* dysbiosis can produce 5-reductase, which significantly impacts testosterone [20].

Schizophrenia is more common in men than women at age 40, but it is more common in women after that age. In male patients with schizophrenia, elevated *C. albicans* was associated with GI disturbance, and by using probiotics, the GI disturbance improved, and the *C. albicans* level was reduced, but this change was not observed in females who were treated with probiotics [21].

Women are twice as likely as men to suffer from depression. A study found that females with depression had a higher abundance of *Actinobacteria* than healthy participants, while males with depression had a lower abundance of *Bacteroidetes* [21], [22].

The fecal cultures revealed that the anti-inflammatory drug indomethacin affects the microbial environment in women but not men. Female patients with metabolic syndrome had a lower abundance of *Faecalibacterium* than male patients [22].

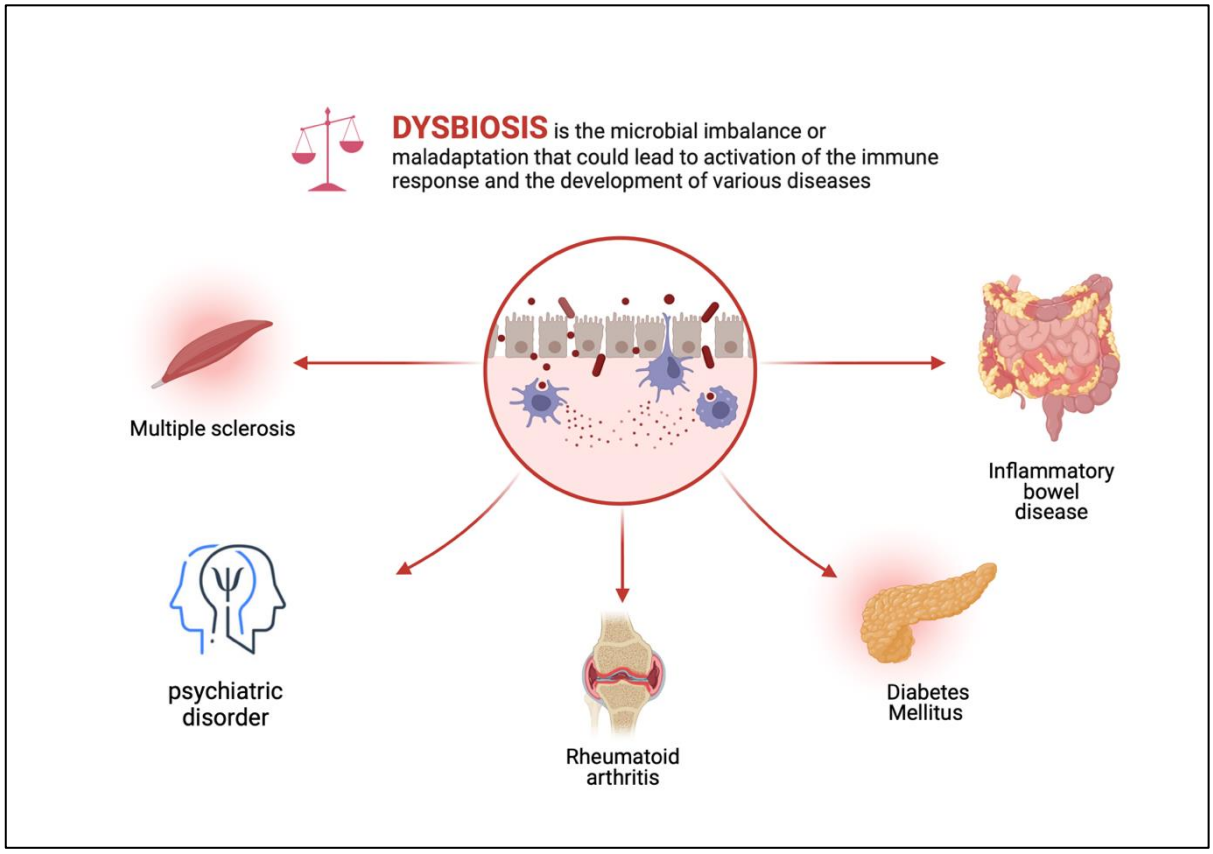

Figure 2. The schema represents various disorders that are influenced by an imbalance in the gut microbiota [1], [2].

5. Altered Gut- Brain axis in neuropsychiatric diseases

5.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative condition that results in dementia and is marked by the loss of neurons and cognitive impairment. This disease has two pathogenic factors that make it unique. The pathogenic etiology of this condition is the accumulation of β-amyloid through the aggregation of amyloid precursor protein cleavage and the development of neurofibrillary tangles (NFTs), which result from Tau hyperphosphorylation. Chronic inflammation in the brain caused by the presence of these chemicals results in the release of microglia. Reactive oxygen species, nitric oxide, and cytokines are just a few of the harmful and pro-inflammatory effects it stimulates β-amyloid buildup, and poor amyloid clearance results from chronic inflammation. Adverse effects include neurodegeneration and impaired cognition [23]. As they work to reduce the inflammation and blood-brain dysfunction, astrocytes attempt to return the brain to its normal physiological state [18]. During the Aging decrease, the number of microbiomes such as *Bifidobacterium* and *Lactobacillus* while the Dysbiosis as *fusobacteria*, *Propionibacteria,* and *clostridia increases* [3].

Stress is one of the elements that have a significant impact on the microbiome environment. *Citrobacter rodentium* infections are associated with stress, even though wild-type mice are not affected by these bacteria in terms of memory or cognition. Surprisingly, giving this type of bacteria for a week can stop alterations brought on by stress. Diet is another element that affects the gut ecosystem. Fruits and vegetables can lower the risk of cognitive impairment. The Mediterranean diet has been shown to protect against and reduce the risk of cardiovascular disease and can help lessen cognitive impairment. While eating junk food and meat is linked to decreased cognitive abilities and an increase in inflammation. It has been suggested that combining a high-fat diet (HFD) with some probiotics will help improve cognitive impairment. *Bifidobacteria* or *Lactobacillus* strains with HFD were the probiotics that were utilized [3].

The outer layer of Gram-bad bacteria's cell wall, known as lipopolysaccharides (LPS), contributes to AD inflammation. As it binds to CD14 of the Toll-like receptor 4 (TLR), which is expressed on microglia, it enhances β-amyloid fibrillogenesis and causes an inflammatory response [24]. Gut microbiomes influence the oxidative stress system. Nitrite can be converted into nitric oxide by *Lactobacillus, E. coli*, and *Bifidobacterium*, which enhances the blood-brain barrier's permeability (BBB). As a result, nitric oxide and superoxide reacted to form

peroxynitrite, which is toxic to AD neurons. Given that β-amyloid increases oxidative Stress, there is evidence linking the two to β-amyloid formation and aggregation. Dysbiosis, such as *Salmonella* and *E. coli*, can use sulfur amino acids to create hydrogen sulfide in the gut, which promotes the upregulation of the genes for proinflammatory mediators like IL-6. Anaerobic cocci create hydrogen gas, which has anti-inflammatory and antioxidant properties. It has been noted that gut dysbiosis may reduce hydrogen synthesis and limit the availability of the gas to brain neurons [25].

In contrast, accumulation results in a limit for SCFA building. Simultaneously, research has been done on the interactions between bacteria that produce hydrogen and hydrogen-eating microbes like *Methanobrevibacter smithy*. Methane is another gas with anti-inflammatory, antioxidant, and anti-apoptotic properties. It can combat an elevated level of superoxide dismutase and reduce levels of malondialdehyde and 3-nitotyrosine [25].

The disruption of gut microbiota is another element that needs to be considered. The synthesis of short-chain fatty acids (SFAs), such as acetate, butyrate, and propionate, impacts the brain and regional gastrointestinal function. SFAs are a crucial substrate for the synthesis of ATP and mitochondrial respiration. In addition to providing energy, they prevent histone deacetylases from changing how particular cellular proteins are expressed. SFAs inhibit neuron activity by interacting with specific G protein-coupled receptors (FFAR3 and FFAR2: free fatty acid receptors 3 and 2) [26].

Chronic inflammation is the pathophysiological hallmark of Alzheimer's disease. *E. coli* strains, *Salmonella, Shigella, Helicobacter pylori, Vibrio, Clostridium,* and *Bacteroides fragilis* are among the bacteria that cause gut dysbiosis. These exotoxins affect epithelial colon cells by lowering the expression of a protein that forms tight junctions, which increases gut permeability. Additionally, pro-inflammatory cytokines and factors are stimulated by allowing microbial metabolites to enter the circulation. These substances can then pass the blood-brain barrier (BBB) and activate microglia and astrocytes [3]. The production of extracellular protein fibers forms a biofilm with a structure like cerebral amyloid that is recognized by the same TLR2/TLR1 receptor system and can activate inflammatory factors like IL-17 and IL-22 as a defense mechanism to protect the bacteria against change in the surrounding stressed environment. However, their amino acid sequences are different [26]. The main factor controlling chronic inflammation in AD is the interaction between TLRs and the receptor for advanced glycation end-products (RAGE). The amyloid protein and lipopolysaccharides 9 activate RAGE. The bacterial amyloid, known as "curli fibers," can be produced by *E. coli*

K12. The TLR2 receptor can detect the subunit GA amyloid precursor, which is a crucial component in its formation [27].

There is a fundamental link between type 2 diabetes and Alzheimer's disease (AD). First, insulin promotes the production of β-amyloid from the intracellular neuronal compartment, which increases inflammation in the central nervous system (CNS). Second, the β-amyloid aggregation disrupts insulin receptor signaling, increasing the activation of glycogen synthase kinase-3-amyloid, enhancing the formation of β-amyloid and tau hypophosphorylation [27].

Antibiotic use is beneficial in the treatment of AD. Cefepime can pass the blood-brain barrier (BBB), which may be detrimental to cognition and congenital status without harming the gut flora. Omeprazole, Clarithromycin, and Amoxicillin, a triple anti-Helicobacter pylori medication, enhances mental performance metrics in AD patients. Rapamycin demonstrates its efficacy in lowering Tau phosphorylation because the pathogenic mechanism of AD is favorably impacted by the activation of the mTOR signaling pathway. After taking doxycycline and rifampin together, patients with mild to moderate dementia saw successful improvements in AD. Antibiotic resistance must be considered, even though it can be obtained via antibiotics in AD [28].

Probiotic milk supplementation (200 ml/day) containing a combination of (*Lactobacillus acidophilius, L. casei, Bifidobacterium bifidum, and L. fermentum;* 2 x 109 CFU/g each strain) for 12 weeks to improve cognitive function and insulin metabolism without affecting the lipid profile and inflammatory system is one potential supportive therapy for AD. Another combination that improves the gut status in AD patients is (*L. casei W56, L.acidophilius W22, B.lactis W52, L.paracasei W20, L.plantarum W62, Lactoccus lactis W19, B.lacctis W51, B.bifidum W23, and L.salivarius W24*) for 28 days. Memory is improved by taking probiotic capsules for 12 weeks that contain *L. fermentum, L. plantarum, and B. lactis or L. acidophilus, B. bifidum, and B. longum* (3 _109 CFU) [24]. Due to its anti-inflammatory, antioxidant, and anti-apoptotic qualities, hydrogen is intended to be used as a therapeutic medicinal gas produced by anaerobic cocci and some strains of *Clostridium* and *Enterobacteriaceae* [25]. Lactulose is one of the most traditional products for treating constipation. However, it also improves learning and memory, can control the gut flora, and lessens neuroinflammation. The precise mechanism has not yet been determined. The oral Preparate sodium oligomannate (GV-971) prebiotic has been approved to treat mild to moderate AD in China. It enhances cognitive function and permeates the blood-brain barrier, attaching directly to β-amyloid and inhibiting the production of β-amyloid fibrils. It comprises

marine brown algae-derived acidic linear oligosaccharides [10]. Rifaximin has been shown to be effective in treating mild bacterial infections of the intestine and motor irregularities [29].

The application of gastrointestinal nematodes and the use of microbial proteins secreted by these nematodes as a new type of immunotherapy to treat AD have been proposed because their infection under stable conditions disturbs the environment of the gut microbes and rearranges its balance, which causes the dysregulation of immune response in the gut and restores the healthy flora. An experiment on mice revealed that *Heligmosmoides polygyrus* nematode infection could stop *Bacteriodes vulgatus* growth and shield mice from intestinal inflammation [26].

5.2. Parkinson´s disease

Synucleinopathy, a neurodegenerative condition that causes Parkinson's disease (PD), has a substantial impact on the bidirectional connection between the brain and the gut. The Parkinson's disease signature Lewy bodies, which are the product of intracellular eosinophilic inclusions, are present and dopaminergic neurons in the substantia nigra pars compacta (SNc) are experiencing a degenerative decline. The primary factor in the formation of Lewy bodies is the accumulation of insoluble misfolded α-synuclein. The spinal cord, peripheral neurons, sympathetic ganglia, enteric nervous system (ENS), salivary glands, adrenal medulla, vagus nerve, cutaneous nerves, and sciatic nerve are all affected in addition to the brain [30]. The control of visceral blood flow and gastroprotection are essential functions of sensory neurons. Nitric oxide (NO) is stimulated through the action of the released capsaicin, which inhibits the inflammatory response. Through neuro-glial circuits in the myenteric and submucosal plexus or by the action of sympathetic and parasympathetic on the gut, the ENS regulates many functions of the gastrointestinal tract. The alteration in gut microbiomes alters the nature of this communication because the Brain-Gut axis is tied to it. Toll-like receptor (TLR) ligands, which promote the pro-inflammatory impact, can be produced by the gut flora [30].

90% of the serotonin that regulates gut motility, emesis, visceral hypersensitivity, and secretion is produced by the enterochromaffin cells. Serotonin and its metabolism in the liver can be controlled by the gut microbiota. Dysbiosis, on the other hand, secretes neurotoxic substances including D-lactic, ammonia, or neurotoxins like *Clostridium perfringes, Clostridium botulinum, Clostridium butyricum,* and *Clostridium baratii*. These dangerous chemicals enter the body through the spinal nerves and brainstem's systemic circulation [22].

Peptic ulcers brought on by Helicobacter pylori are common in people with Parkinson's disease. It was unable to confirm the existence of H pylori due to the symptoms of dyspepsia and gastric irritation, either as non-motor symptoms of PD or as a side effect of levodopa [23].

Constipation, which is connected to microbiota makeup and their metabolites, is the primary complaint of PD patients. Leaky gut syndrome, which is caused by a problem with gut barrier function and facilitates the easy supply of microbial metabolites to the brain, contributes to increasing neuroinflammation and damage in SNc and has been linked to α-synuclein pathology in the early stages of Parkinson's disease (PD) [23].

It is discovered in the faeces of PD patients with a high abundance of *Enterobacteriaceae* and a low abundance of *prevotellaceae* bacteria. *Prevotellaceae* bacteria can make mucin and secrete thiamine and folate in the gut mucosal layer. Low levels of *Prevotellaceae* were discovered together with a high level of the gastrointestinal hormone ghrelin. Another finding is that *proteobacteria, Lactobacillus*, and the species *Ralstonia* are highly prevalent in the mucosal and faecal microbial makeup, while *Blautia, Coprococcus, Roseburia, Clostridium coccoides, Bacteroides fragilis*, and the genus *Faecalibacterium* are less prevalent [30]–[32]. A different clinical investigation revealed a high prevalence of the *Rumminococcaceae* family's *Akkermansia* and a low prevalence of the *Lachnospiraceae* [31], [32].

As a result of the inflammatory response against misfolded α-synuclein activating microglial cells in the SNc, neural cells and oligodendrocytes generate oxidative stress, which reacts with microbial TLR2, resulting in an increase in TNF and IL-1 production as well as TLR expression. This causes dopaminergic neurons in the SNc to die [30].

The gut microbiome governs the development and operation of microglia. By changing pro-inflammatory and inflammatory cytokines, modification in the microbiota indirectly affects how the microglia function. Additionally, the alteration in gut flora affects the activation of toll-like receptors, which can detect the antigenicity of microglia like LPS [23]. According to a study, PD patients had high levels of Lactococcus bacteriophages, which are lactic acid bacteria that create dopamine and regulate intestinal permeability [32].

A high-energy and high-sugar diet has been found to worsen gut dysbiosis, cause inflammation, and upset the brain-gut axis. *Prevotella* and *Paraprevotella* levels are lower when carbohydrates and fibres are consumed than when animal fat and protein are consumed. A reduced abundance of *Bifidobacteria* and a higher abundance of *Firmicutes* and *Proteobacteria* are linked to the Western diet. *Leuconostoc mesenteroides* and *Leuconostoc lactis* are linked to healthy *Leuconostoc lactis* and sour milk consumption. Contrarily,

consuming whole milk reduces diversity [24]. The abundance of *Ruminococcus*, *Atopobium,* and *Enterobacteriaceae* is increasing, while the abundance of *Lactobacilli, Bacteroides, Prevotella,* and *Faecalibacterium prausnitzii* is decreasing because of aging [32].

It has been established that smoking and coffee use lessen the risk of PD. *Bacteroides* and *Prevotella* bacteria are becoming more prevalent due to the metabolism of dietary fibres in coffee, which produces SCFAs. Drinking coffee lowers the abundance of *Clostridium* spp. and *E. coli* while raising levels of the anti-inflammatory bacteria *Bifidobacteria* [24]. In addition to this proof, there is an essential link between *H. pylori* infection and the development of PD clinically [31]. The gut microbiomes are disrupted by conventional PD medications, particularly catechol-o-methyltransferase (COMT) inhibitors and anticholinergics. A high level of *Lactobacillaceae* and a low level of *Clostridiales Incertae Sedis* IV were related to COMT inhibitors' usage. Another study found a link between a low level of the genera *Dora* and *Phascolarctobacterium* and a daily dose of levodopa. However, another study shows that there is no connection between the use of drugs and the population of the microbiome [32].

The various therapies are diverse. A dietary supplement is one of them. Omega-3 fatty acids, a polyunsaturated fatty acid, have an anti-inflammatory impact and decrease the build-up of α-synuclein. The ability of ginseng extract to reduce inflammatory factor (IL-6 and TNF-α) release has been demonstrated. The flavonoid silymarin boosts TLR4 activation and antioxidant activity. Probiotics such as *Lactobacillus rhamnosus, Lactobacillus casei Shirota, and Lactobacillus reuteri* supplementation are other options for treating PD. Another aspect is using prebiotics such as inulin, galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), and SCFAs in treating PD. One of the logical requirements for treating Parkinson's disease is the use of antibiotics. Minocycline is one of the antibiotics that can pass the blood-brain barrier and prevent dopamine from depleting in the striatum and nucleus accumbens. Caspase-1 expression and NO release are both decreased by minocycline. A further potential antibiotic is neamine, an aminoglycoside that can lessen BBB permeability and apoptosis [23]. TLRs modulators, such as the cyclic nucleotide phosphodiesterase inhibitor (Ibudilast) and the TLR4 antagonist used to treat asthma and post-stroke vertigo, are one of the most effective treatments for Parkinson's disease (PD). Eritoran tetrasodium is another TLRs modulator that prevents the release of pro-inflammatory cytokines caused by LPS [22].

5.3. Schizophrenia

Psychosis is one of the clinical symptoms of schizophrenia. Although the pathogenesis of this psychiatric condition is not entirely understood, it has been noted that the expression of brain-derived neurotrophic factor (BDNF) and the activity of the N-methyl-d-aspartate (NMDA) receptor have decreased in the cortex and hippocampus. It was found that using non-steroid anti-inflammatory medications could lessen the severity of the disease, indicating a relationship between schizophrenia and inflammatory response. Toll-like receptors are a vital component of the immune response (TLR). Lipopolysaccharides (LPSs), a component of gram-negative bacteria's cell walls, cause TLR to react. TLR carries out the preservation of intestinal epithelial hemostasis. The metabolic pathway of tryptophan plays a part in the etiology of schizophrenia. Kynurenic acid is a tryptophan metabolite and an NMDA receptor antagonist. Relapse was associated with lower peripheral kynurenic acid levels than those in the central nervous system. Furthermore, in schizophrenia patients with autoimmune diseases, anthranilic acid levels increased while kynurenic acid levels decreased. Tryptophan metabolism is significantly influenced by gut microbiomes [33].

The gut microbiomes either modify the gut immune response or directly interact with neurological and endocrine pathways to influence the etiology of schizophrenia. The activation of microglia in the hippocampus, white matter, cingulate, and neocortex by SCfAs, particularly propionic acid, upsets the harmony between excitation and inhibition in brain circuitry by increasing glutamatergic and decreasing GABAergic transmission. The hypothalamic-pituitary-adrenal (HPA) axis is regulated by the microbiomes as well, and this is accompanied by an increase in corticotrophin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), cortisol, and aldosterone levels [34].

Through the overproduction of glucocorticoids, there is a link between schizophrenia and HPA dysfunction. Stress, whether physical or mental, causes the hypothalamus to release the cortisol-releasing hormone (CRH). ACTH is released when CRH connects to receptors on the anterior pituitary gland. As a protective mechanism, cortisol limits the release of GC due to stimulating the adrenal cortex to release cortisol. The hypothalamus is significantly impacted by schizophrenia's elevated levels of GC release. In schizophrenia patients, an elevated quantity of GC causes the hypothalamus to become inflamed [28].

Cytokine peripheral signaling can influence some neurons, including microglia and astrocytes. BBB leaks include active trafficking via transport molecules, stimulation of the

HPA axis, and recruitment of activated cells such as peripheral monocytes or macrophages. Functional lymphatic veins lining the Dural sinuses allow immune cells to connect with the brain. Peripheral cytokines can also influence neurogenesis or synaptic development, impacting mood and cognition. After looking at a serological indicator of bacterial translocation, it was shown that schizophrenia had a high level of sCD14. Additionally, the blood antibody levels of the fungi *Saccharomyces cerevisiae* and *Candida albicans* were elevated. Enhanced permeability of the intestinal lumen is proposed as the rationale for this distinct serological signature (leaky gut) [34].

The stress resulted in bacterial invasion and elevated plasma lipopolysaccharide by leaky gut. Through this opening, cytokines can pass through the BBB, enter the brain, interact with the hypothalamus and circumventricular organs, and influence IL-1, IL-6, and HPA axis function. To attack foreign, invaders, mobile, branching immune cells called microglia, which are needed to be stimulated by the release of cytokines. Long-term activation causes synaptic damage and neuronal death, increasing the likelihood of developing schizophrenia [29], [30]. An endogenous protein with anti-inflammatory and immunosuppressive characteristics is called Clara cell protein (CC16). It also inhibits the IL-1 and interleukin 6 (IL-6) receptors. Schizophrenia patients were shown to have high CC16 serum levels [35].

More than 100 distinct genetic loci are associated with schizophrenia, making it a polygenic psychiatric illness. Rare and recurrent copy numbers (CNVs), also known as single nucleotide polymorphisms (SNPs), play a crucial influence in raising the risk of schizophrenia. Pleiotropy is another dangerous genetic component or the possibility that one gene may impact several phenotypic traits. The genes encode synaptic proteins, and the postsynaptic density protein contains many uncommon DNA mutations, CNVs, SNPs, and indels that alter the expression of glutamate receptors, voltage-dependent calcium channel protein, a microtubule-associated protein, and dopamine receptors. Human leukocyte antigen (HLA) and schizophrenia are strongly correlated. It is a potential risk factor for schizophrenia because it plays a large part in antigen-presenting peptides for T-cell receptors, which participate in neurological processes like memory development and behavior [36].

Synaptic plasticity is significantly influenced by glutamate and its receptors, particularly ligand-gated ionotropic glutamate receptors (iGluRs). Schizophrenia is linked to iGluRs signaling disruption. Some gut bacteria, including *Campylobacter jejuni, Corynebacterium glutamicum, Brevibacterium lactofermentum, Bacillus subtilis, and Brevibacterium avium,* are linked to glutamine metabolisms [36].

A class of biochemicals known as neurotrophic factors (NTFs) is responsible for neurons' development, growth, and maturation. Numerous investigations have found that congenital microbial infection in a fetus raises the likelihood of schizophrenia developing [30].

BDNF is a neurotrophin that aids learning and memory functions and neurodevelopment in the hippocampus, cortex, and basal forebrain. Low levels of BDNF have been found in post-mortem hippocampus samples and plasma samples from schizophrenic patients. According to research, higher levels of BDNF were associated with higher levels of *Lactobacilli* and *Actinobacteria* and lower levels of *Proteobacteria* and *Bacteroidetes* [31]. With the aid of chronic cytokine-mediated inflammation and directly releasing lipopolysaccharide or SCFAs, gut dysbiosis can increase cortisol release and sensitivity [28]. These SCFAs impact the amygdala's structure through circulation, which affects emotional learning and social behavior. Early life stress lowers BDNF levels and glucocorticoid receptors (GR) expression in the hippocampus, indicating that early life stress raises the risk of schizophrenia [28].

The bacteria in the gut can produce a variety of neurotransmitters, including *Lactobacillus* and *Bifidobacterium*'s production of γ -aminobutyric acid (GABA), *Escherichia, Bacillus,* and *Saccharomyces* spp. productions of nonadrenal, *Bacillus*' production of dopamine, *Lactobacillus*' production of acetylcholine, and *Escherichia, Clostridium, Burkholderia, Streptomyces, Pseudomonas, and Bacillus* all carry out tryptophan metabolism [37].

It has been found that schizophrenia causes a drop in *Faecalibacterium* abundance, which causes a rise in TH17 cells. The hippocampus's microglia are expected to be activated by these cells, which results in aberrant behavior. A correlation between the severity of schizophrenia and an increase in *Veillonellaceae* and *Lachnospiraceae* abundance was discovered. Additionally, since lactic acid-producing bacteria are seen to be expanding, as well as their anti-inflammatory action [29], [30].

Although there was a decrease in *Coprococcus, Roseburia, Blautia,* and *Proteobacteria,* it was shown that schizophrenia patients had a significant abundance of *Succinivibro, Megasphaera, Collinsella, Clostridium, Klebsiella, Methanobrevibater, Haemophilus,* and *Sutterella* [30].

Additionally, it was discovered that the oropharyngeal samples from schizophrenia patients had higher levels of lactic acid bacteria (*Lactobacilli and Bifidobacteria*), *Candida,* and *Eubacterium,* with lower levels of *Neisseria, Haemophilus,* and *Capnocytophaga*. Oral infection with gram-negative, anaerobic bacteria and the implantation of the microbe in tooth

plaque are two features of the polymicrobial inflammatory condition known as periodontitis. *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Tannerella forsythensis, Eikenella corrodens*, and *Treponema denticola* are the bacteria that predominate in oral periodontitis. Due to the activation of microglia, T lymphocytes, and proinflammatory mediators by periodontitis, neuroinflammation is a substantial contributor to the etiology of schizophrenia. That explains how oropharyngeal infection and schizophrenia are related [38]. In samples taken from schizophrenic patients, bacteriophages virus was found in addition to oral bacteria. In these samples, lactobacillus phage phiadh predominated as well. However, it was crucial to note that patients with immunological disorders such as diabetes or those using the drug valproate were associated with the existence of bacteriophages [39]. Some fungi, such as an increased prevalence of *Candida albicans* and *Saccharomyces cerevisiae*, were linked to schizophrenia [39]. It has been discovered that because fermented foods enhance cognitive function, diet can alter human behavior. Gluten-free diets improved the behavior of schizophrenia patients who have abnormal sensitivity to gluten and bovine casein [34].

The gut bacteria can be killed by the antipsychotics' antibacterial capabilities. Studies demonstrated the efficacy of flupentixol, thioridazine, and chlorpromazine as antibiotics. The intestinal permeability, bile salt production, and pH of the gastrointestinal tract can all be altered by antipsychotic medications, which impact drug absorption. This impacts some antipsychotic medications' extended formulations, such as quetiapine's extended release. Because of this, it is advised that the extended-release antipsychotic medication be administered intravenously or intramuscularly [40]. *E. coli* can be filamented by phenothiazine antipsychotics, which also prevents the organism from adhering to intestinal epithelial cells. *Bifidobacterium* and *Escherichia coli* are more prevalent when using risperidone, whereas *Lactobacillus* and *Clostridium coccoides* are less prevalent. The prevalence of *Lachnospiraceae, Akkermansia,* and *Sutterella* was reduced by antipsychotics like risperidone, aripiprazole, and olanzapine [29].

Like antipsychotic medications affect the gut flora, the gut microbiomes influence the drugs. Drug distribution, metabolism, excretion, and absorption are all impacted by gut bacterial enzymes. For instance, the colon bacteria metabolize the isoxazole found in the Benzisoxazole ring of the risperidone molecule. The microbial enzyme can potentially alter the expression of glutathione S-transferases and cytochrome P450 indirectly. As previously mentioned, the pharmacodynamics of medications are indirectly impacted by the production of neurotransmitters by the gut flora [40].

Prebiotics are one of the therapeutic alternatives, as usual. Non-digestible fructan oligosaccharides (FOS) and galactan oligosaccharides are common prebiotics (GOS). The Brief Assessment of Cognition in Schizophrenia measures global cognitive performance, which is improved by the prebiotic formulation B-GOS® (BACS). Although the B-GOS® mechanism in schizophrenia is not entirely known, mice have higher levels of BDNF. A probiotic supplement containing vitamin D, *Lactobacilli*, and *Bifidobacterium bifidum* raises the plasma's total antioxidant capacity, decreases CRP levels, and improves overall and general PANSS scores [41].

Tetracycline- or minocycline-containing antibiotics effectively ease the unpleasant symptoms in patients with early-stage schizophrenia [15].

Weight gain is the primary adverse effect of antipsychotic medications. Obesity and schizophrenia have a tangled link. Olanzapine caused weight gain and was associated with a decline in *Bacteroides* and an increase in *Firmicutes*. The issue is that obesity is associated with worse cognitive performance, but it is unclear whether this is due to a change in kynurenate levels or a change in BDNF [41].

5.4. Depression

Although the biology of depressive disorder is unknown, numerous theories explain it. The most prevalent explanation holds that the synaptic cleft has lower serotonin, noradrenaline, and dopamine levels than usual. The effectiveness of antidepressant medications supports this theory [42]. Neurotransmitters may have changed, as evidenced by the hyperactivity of the glutamatergic and cholinergic systems and the suppression of the γ-aminobutyric acid system (GABA). Some brain regions, like the prefrontal cortex and hippocampus, are less functional in depressed sufferers; nevertheless, the amygdala is more active. Additionally, BDNF levels drop, which causes neuron death. Chronic elevations in GC and ACTH in depressive patients cause disturbance in the HPA system. Additionally, recent studies suggested that the HPA system's malfunction causes a decrease in BDNF expression, an inhibition of 5-HT production, a decrease in the expression of Glu receptors, and a disturbance of neuroplasticity [43].

As evidenced by the high levels of IL-1, IL-6, and TNF-α in depressive patients, the immune system and its inflammatory components play a crucial role in the onset of depression. As previously stated, Toll-like Receptors recognize pathogen-associated molecular patterns (PAMPs), such as LPS, as the target for inflammation (TLRs). This causes pro-inflammatory

factors like IL-1, IL-1, TNF-α, and IL-6 to become active. These cytokines produce TH1 and TH17 cells. Bacteroides fragilis secretes the polysaccharides, which promote the growth of TH1 cells. These inflammatory substances penetrate the BBB and go to the brain [42]. In depressive individuals, there is an increase in IL-6 and TNF levels and a drop in IL-10 and TGF levels, which suppress the HPA system's negative feedback, increase BBB permeability, decrease 5-HT production, and disturb the glutamatergic system. As neuroglia malfunction results in depression, neuroglia cells play a vital role in regulating neuroimmune and neuroplasticity [43].

Enterochromaffin cells in the intestine use the serotonin (5-HT) produced in the gut, which accounts for 90% of the body's serotonin supply. Gastrointestinal functions are significantly influenced by intestinal serotonin. Antibiotic use reduces the amount of gut bacteria, which is linked to an increase in the amount of tryptophan in the blood, which raises the level of 5-HT in the hippocampal hippocampus. By altering tryptophan in its amine form, tryptophan decarboxylases help the gut microbiomes harvest tryptophan from the diet, which controls mood and behavior [44]–[46].

Crucial molecules in the serotonin generation through tryptophan are SCFAs, produced by gut microbiomes. Indoleamine-2,3, -dioxygenase (IDO) and tryptophan-2,3, -dioxygenase (TDO) enzymes convert tryptophan to serotonin. IL-6 and interferon-gamma (INF-γ) promote the alteration in tryptophan metabolism. IFN- γ, IL-2, and TNF- α are cytokines that increase the likelihood of depression. It was shown that *B.infantis* increased plasma levels of tryptophan while also reducing IDO activity. *B.infantis* also demonstrated anti-depressive action. Additionally, tryptophan plays a crucial part in the metabolism of kynurenine. Its metabolism has two distinct pathways: either the formation of quinolinic acid (QUIN), a neurotoxin and NMDA receptor antagonist, or the production of kynurenic acid (KYNA), a neuroprotector and NMDA receptor antagonist [42],[47],[46].

Patients with depression have elevated levels of a specific SFA called isocaproic acid in their feces. Butyric acid, another SFA, prevents hippocampus microglia from activating and histone deacetylating. Microglia are activated by butyric acid at low concentrations. Consequently, this induces neuroinflammation and depressive-like behaviors [47].

Dopamine is a critical neurotransmitter in controlling anhedonia, a crucial component of depression. In depressive patients, it was shown that there was a lower amount of dopamine transporter binding and striatal dopaminergic activity. Intestinal secretion and motility are both impacted by dopamine. *E. faecium* modifies the gut immune system using the dopaminergic

pathway [44], [45]. Unfortunately, there have been few investigations on the effects of noradrenaline on the microbial gut in depression patients [45].

The effect of microbiota on the intestinal immune system in depression was thoroughly demonstrated in an ovarian cancer patient with mild, moderate, and severe depression, as the levels of lymphocytes and CD4+ were significantly different, and immune activity was low in patients with severe depression [44].

A decrease in BDNF levels is associated with poor neuroplasticity and the development of depression symptoms. Some antidepressants, such as ketamine, increase BDNF activity via mTOR signaling [44], [48].

Oxidative stress plays a role in depression because it is linked to neurotransmitter metabolism, neuroplasticity, and neuronal apoptosis, which is essential in depression. By generating antioxidants, the microbial gut controls oxidative stress. Disruption of gut microbiomes reduces antioxidant levels, which increases the etiology of depression [49].

It was found to have a high abundance of *Bacteroidetes, Proteobacteria, Actinobacteria,* and *Prevotellaceae*, and a low abundance of *Firmicutes, Bifidobacterium, Lactobacillus, Faecalibacterium, Lachnospiraceae*, and *Ruminococcaceae* [43], [44], [50], [46]. In addition, low abundance of *Coprococcus, Dialister*, and *Sutterella*, while there is an increased abundance of *Actinobacteria* and *Eggerthella* [51].

The most significant risk factor for depression is antibiotics; however, this risk is dose- and time-dependent. Ceftriaxone and minocycline both have antidepressant properties [43]. Antibiotics can modulate emotions in the human body. A study found a link between using levofloxacin in combination with trimethoprim-sulfamethoxazole and suicide attempts in a 75-year-old man. Penicillin, fluoroquinolones, and quinolones have been linked to an increased risk of depression. The activation of microglia and astrocytes is linked to the beginning of the depression and results in glial cell alterations. The observation of glial cell activation following antibiotic treatment was surprising [49].

Stress is another risk factor for depression development because chronic stress changes the gut microbiomes, resulting in a smaller hippocampus, lower levels of 5-HT, lower levels of BDNF, higher levels of stress hormones, and lower levels of IL-10 [37]. Depression is linked to HPA axis hyperactivity caused by stress, which manifests as elevated CRH and decreases ACTH levels. Stress also increases the intestine's permeability to water, salt, and endotoxin [43]. There is a relationship between depression and HPA axis hyperactivity caused by stress, as measured by increased CRH and decreased ACTH levels. In addition, stress increases intestinal permeability to water, salt, and endotoxin [50].

Women are more sensitive to stress than males, as evidenced by a higher level of IDO in women than in men. This explains why women have a higher risk of depression than males. In addition to stress, other factors that cause inflammation include somatic symptomatology, interpersonal stresses, childhood diversity, and obesity [50].

Diet is important in depression since the Western diet is high in saturated fat, sugar, and food additives. As a result, the microbial gut is disrupted, and the incidence of depression rises [43]. Long-term Western food intake inhibits SFA production, increases systemic inflammation, particularly in the brain, and increases some bacteria species, resulting in the creation of neurotransmitters and neuromodulators such as GABA, NE, 5-HT, DA, and acetylcholine. As a result, brain activities are regulated [48]. Administered high-fat and animal protein is correlated to an increased abundance of *Actinobacteria* [51].

Antidepressant medicines alter gut microbes. The tricyclic antidepressant can prevent the growth of *E. coli, Yersinia*, and *Plasmodium*. Gram-positive bacteria can be inhibited by selective serotonin reuptake inhibitors (SSRIs). Additionally, the antidepressant ketamine can suppress the growth of *Staphylococcus, Enterococcus,* and *Candida albicans* [43].

Probiotics are helpful in the treatment of depression. The *B. longum* therapy relieved the stress. Chronic *L. rhamnosus* use appeared to have a positive effect on depression [50]. Bimuno-GOS (a GOS preparation treated with galactosidase enzyme derived from *Bifidobacterium bifidum*) consumption lowers cortisol while increasing *Bifidobacterium* and *Lactobacillus* in the gut. *Antrodia cinnamomea*, a fungus used in Chinese medicine, demonstrated anti-obesogenic and anti-inflammatory properties as well as alleviated depression-like symptoms [48].

5.5. Autism

Autism, also known as an autism spectrum disorder (ASD), is a complex condition characterized by social difficulties such as repetitive behavior, poor communication, and difficult speech. This disorder's risk factors are either genetic or environmental, but many cases are idiopathic. Constipation is the most observed symptom in autistic children. In addition, sleep disturbances and aggression are reported. Disaccharide absorption and metabolism were disrupted in the guts of autistic children. The ileum showed low activity of sodium-glucose cotransporter (SGLT1) and glucose transporter 2 (GLUT2), indicating malabsorption in the intestine. The bacteria in the intestine ferment the small molecular sugars, causing osmotic

diarrhea and bloating. The severity of autistic behaviors was linked to GI disturbance. Autism was characterized by increased intestinal permeability due to low expression of barrier-forming proteins in tight junctions and high expression of pore-forming proteins. As a result, bacterial metabolites such as LPS can easily cross the BBB and reach the brain, increasing brain inflammation due to high cytokine levels [10].

The expression of some claudins (CLDN), such as CLDN-5 and CLDN-12, has been observed in the brains of autistic children. CLDN-5 is a critical protein in tight junctions for endothelial cell adhesion in the brain. The leakage of both proteins reduces the integrity of the BBB. Autistic patients also have increased microglial cell activity, which causes synapses to malfunction. It has been proposed that arginine vasopressin, released during brain inflammation, influences social behaviors in autistic children. The structural change in the brain was caused by an increase in the number of neurons in the prefrontal cortex and a decrease in the number of neurons in the cerebellum. A high abundance of *Clostridia* spp. was associated with a decrease in the number of Purkinje cells responsible for GABA production [10], [52], [53].

Bacteria are earned during pregnancy when bacteria such as *Enterococcus*, *Streptococcus*, and *Staphylococcus* are transferred from mother to fetus. These bacteria create an anaerobic environment in the gut by consuming oxygen, allowing *Bacteroides*, *Bifidobacterium* spp., and *Clostridium* spp. to colonize. As previously stated, the mode of delivery and breastfeeding both play an essential role in the development of the bacterial environment in the gut [10], [54]– [56]. It is also suggested that the late onset and duration of breastfeeding significantly impact the development of Autism [54]. Any disruption in the gut microbiome causes a leaky gut and activates the immune cells in the gut. Maternal infection during pregnancy affects gut bacteria and may raise the risk of autism development. A high risk of having autistic children was linked to viral infection during the first trimester and bacterial infection during the second trimester [10]. Dysbiosis and impaired intestinal barrier function have been observed with improvement in ASD-relevant behavior after treatment with *Bacteroides fragilis* by enhancing T helper 17 cells, which leads to induction of IL-10-producing T regulatory cells in a maternal immune activation (MIA) model of autism [56], [57]. There is an increase in cytokines and chemokines such as interferon- γ, IL-6, IL-, IL-12p40, tumor necrosis factor alfa, monocyte chemoattractant protein-1, transforming growth factor-, and chemokine (C-C motif) ligand 2 as an immune response in Autism. Microglial cell activity is high in the cerebral cortex and cerebellum of postmortem ASD brains. Furthermore,

autistic children have lack of regulatory T-cells and other T helper cell subtypes [53], [55], [56].

According to the observation of the bacteria population in Autism, a decreased ratio between *Bacteroides* to *Firmicutes* and a low abundance of *Fusobacteria* and *Verrucomicrobia* were observed in fecal cultures of autistic children. In comparison, there is a high abundance of *Akkermansia muciniphila, Anaerofilum, Barnesiella intestinihominis, Clostridium* spp., *Dorea* spp., the family *Enterobacteriaceae, Faecalibacerium* spp. (especially *F. prausmitizii*), *Roseburia* spp., *Desulfovibrio* spp., *Clostridia* spp., *Parasutterella excrementihomonis, Prevotella copri, Prevotella oris,* and *Turicibacter* spp. Other high abundance bacteria in Autism are: *Aeromonas, Odirobacter splanchnicus, Parabacteroides, Porphyromonas, Pseudomonas,* and *Turicibacter sanguinis*. There is a decreased abundance of *Escherichia coli, Bifidobacterium, Fusobacterium, Oscillospira, Sporobacter, Streptococcus, Lactobacillus, Lactococcus, Staphylococcus, Subdoligranulum,* and *Collinsella* spp., except *Collinsella aerofaciens* in Autism [10], [52], [53], [55]– [60]. *Desulfovibro* spp. was linked to autism severity and GI dysfunction because these bacteria can produce hydrogen sulfide, a cytotoxic metabolite to colonic epithelial cells [57]. *Prevotella* spp., which is responsible for plant polysaccharide fermentation and Vitamin B1 synthesis, was found to be in lower abundance in autistic children. The Childhood Autism Rating score (CARs score) was associated with a high abundance of *Clostridium* spp., particularly *Clostridium perfringens*, which produces beta 2 toxin [10]. Many *Clostridiums* spp. was found to be associated with high levels of pro-inflammatory cytokines such as IL-6, IL-1, IL-7, and INF-γ [58]. High abundance of *Escherichia, Shigella,* and *Clostridium* cluster XVIII and low abundance of *Gemmiger* and *Ruminococcus* were observed to be associated to constipation [10], [56], [57]. *Turicibacter sanguinis* is thought to have a serotonin sensor that can break down serotonin [58]. *Candida* spp., particularly *Candida albicans*, has also been found in autistic children. *Candida spp*. cannot grow in a typical gut environment due to competition for nutrients and space. Therefore, *Candida* spp. causes mineral and carbohydrate malabsorption, which is linked to Autism development [10], [52], [53], [57].

It has been observed that ASD is associated with abnormality in the oral cavity and its habituated bacteria. A high abundance of *Haemophilus* and *Streptococcus* spp in dental plaque was observed in ASD, while *Prevotella, Selenomonas, Actinomyces, Porphyromonas,* and *Fusobacterium* were reduced. *Porphyromonas gingivalis,* the most common cause of chronic periodontitis, can be swallowed and alter the gut ecosystem, increasing intestinal permeability and the immune response while also causing systemic inflammation. Oral bacteria can also

enter the brain through routine dental procedures, resulting in bacteremia. When oral bacteria reach the brain, they can reduce anti-oxidative capacity, reducing mitochondria's ability to produce energy [61], [62]. Periodontal infection is more likely because of poor hygiene or as a side effect of medications used to treat Autism, such as psychoactive drugs or anticonvulsants. Phenytoin, for example, has been linked to hypertrophic-hyperplastic gingivitis. Tooth decay, also known as dental caries, is dissolved by acid, which bacteria produce. This acid is produced because of the breakdown of food debris or sugar on the tooth surface. It is suggested that autistic children have a high risk of dental caries due to difficulty brushing their teeth, resulting in poor oral hygiene. Another finding in autistic patients is a lower pH and buffering capacity in their saliva. The importance of a casein-free and gluten-free diet in autism is well documented. By producing urea, protein consumption maintains the buffer balance in salvia [62].

Autistic children have been linked to high levels of serotonin in their blood, due to increased intestinal permeability, as serotonin is known to be synthesized in the intestine and the brain. In autistic children, a high abundance of *Clostridia* spp. was associated with a high level of serotonin. Furthermore, autistic children had a high level of tryptophan, a serotonin precursor. It has been proposed that the cause of sensory hyper-responsiveness in autistic children is a decrease in GABA levels in higher-order motor areas [53]. Glutamate is an essential amino acid in the peptide glutathione, which plays an antioxidant role in the cell and reduces oxidative stress. It is an excitatory neurotransmitter as well. In autistic patients, it is associated with a low abundance of *Bifidobacterium* and a high abundance of *Clostridia*. In samples collected from autistic patients, there was a high concentration of 3-(3-hydroxyphenyl)-3-hydroxy propionic acid, 3-hydroxyphenyl acetic acid, and 3-hydroxyhippuric acid. It is thought that 3-(3-hydroxyphenyl)-3-hydroxy propionic acid lowers the level of catecholamine in the brain, causing Autism. This metabolite has also been linked to the presence of *Clostridia*. After the administration of vancomycin, which is poorly absorbed in the intestine, improved eye contact and reduced constipation [10], [53], [57], [60]. *Clostridiaceae* spp. produce metabolites such as phenols, p-cresol, and indoles, which have toxic effects on human metabolism. P-cresol inhibits the dopamine-beta-hydroxylase enzyme, which regulates dopamine metabolism. P-cresol also competes with neurotransmitters and cofactors in the liver's sulfonation reaction. Because p-cresol is only produced in the gut and is associated with increased intestinal permeability, it can be used as a biomarker for Autism, and the severity of the disease can be determined using it [10], [57], [59], [60]. Zonulin is another enzyme that has been linked to the regulation of intestinal permeability. This enzyme is

abundant in autistic patients [52]. The presence of nicotinamide derivatives in autistic children's urine suggests a change in tryptophan metabolism. The metabolism profile of autistic children revealed a low concentration of kynurenic acid and melatonin but a high concentration of xanthurenic acid and quinolinic acid. Vitamin B6 is a cofactor for the enzyme kynureninase. In Autism, the kynurenine pathway produces a low level of kynurenic acid and a high level of xanthurenic acid and quinolinic [10].

Propionic acid accumulation has a negative effect because it prolongs neurodevelopment and causes seizures. *Clostridia* spp. produces exotoxin and propionate, exacerbating the inflammatory response and worsens autistic symptoms. The reactive nitrogen can react with propionic acid to form 3-nitropropionic acid, a neurotoxin that inhibits succinate dehydrogenase irreversibly. This enzyme is required for the synthesis of NADH. Butyrate has numerous advantages, including acting as an energy source in colonocytes and modulating catecholamine synthase. So, butyrate has a protective effect and is low in autism, whereas propionate, which has disastrous effects, is high in autism [10]. Other mediators, such as melatonin, serotonin, and acetylcholine, essential for brain maturation, are influenced by gut bacteria in Autism [59].

Some toxic elements, such as lead, mercury, arsenic, thallium, and tungsten, have been linked to the severity of Autism. The disruption of gut bacteria has been linked to a persistent lack of iron and zinc. A low iron level causes a decrease in the abundance of *Roseburia* spp. and an increase in the abundance of *Lactobacillus*, as well as a decrease in the levels of butyrate and propionate [60].

Some ASD patients were found to have comorbidities like fragile X syndrome, tuberous sclerosis, or Rett syndrome. The impact of a high abundance of *Faecalibacterium* and a low abundance of *Blautia* on the expression of INF-γ mediated pathways in Autism [10].

Because prebiotics is one of the possible treatments for autism, using galacto-oligosaccharides (GOS) increases the abundance of *Bifidobacteria* and butyrate levels while decreasing propionate levels. The administration of a probiotic cocktail (Children Dophilus) containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* strains improved *Bacteroidestes/Firmicutes* [10]. Another possible probiotic in Autism treatment is the administration of a probiotic mixture of *Lactobacillus rhamnosus*, *Bifidobacterium infantis*, *Bifidobacterium longus*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, and *Lactobacillus paracasei*. *Lactobacillus reuteri* increases oxytocin secretion from the posterior pituitary gland, which improves social behavior. Controlling the amount of gluten and casein in autistic children's diets improves their social and cognitive function [10], [58]. Purified capsular

polysaccharide A (PSA) from *B. fragilis* modulates immune system development and function. That was accompanied by a reduction in Autism symptoms [56], [61]. VSL#3 has been shown to improve GI symptoms as well as ASD symptoms [53]. Some studies have shown that using antibiotics like D-cycloserine and minocycline to treat Autism symptoms is effective. These antibiotics are also neuroprotective because they are partial agonists of the N-methyl-D aspartate receptor and inhibit microglial cell activation [55]. Diet is critical in the treatment of Autism. For 12 weeks, omega-3 FA consumption resulted in a significant improvement in social behavior [53].

5.6. Attention deficit hyperactive disorder (ADHD).

Attention deficit hyperactivity disorder (ADHD) is a common mental disorder in children, characterized by inattention, hyperactivity, and impulsivity. Anxiety and sleep problems are common in children with ADHD. The HPA axis, as a component of the Gut-brain axis, plays a vital role in the pathogenesis of ADHD. The exact pathophysiology of ADHD is still unknown, and more research is needed to comprehend this disease fully.

ADHD pharmacotherapy is effective in the short term, but its long-term effectiveness is still being studied. Side effects are associated with the medications [63]. Methylphenidate, the drug of choice for treating ADHD, stimulates the central nervous system by increasing dopamine and noradrenaline extracellular levels. Insomnia, anorexia, abdominal pain, and headache are some of its side effects. About 10% of patients refuse to take the medication because of its side effects [11], [64].

Changes in neurotransmitters (dopamine, noradrenaline, and serotonin) play an essential role in the pathophysiology of ADHD [63]. Noradrenaline influences bacterial gene expression or bacterial signaling, altering microbial activity. In contrast, some bacteria produce neurotransmitters, such as *Lactobacillus* spp. and *Bifidobacterium* spp. can produce GABA, *Escherichia* spp., *Bacillus* spp. and *Saccharomyces* spp. can produce noradrenaline, *Candida* spp., *Streptococcus* spp., *Escherichia* spp., *Morganella* spp., *Klebsiella* spp. and *Enterococcus* spp. can produce serotonin, *Bacillus* spp. produce dopamine and *Lactobacillus* spp. produce acetylcholine. The prefrontal cortex, striatum dopamine, and noradrenaline pathways are responsible for modulating cognitive control of behavior, motivation, and reward perception [11], [63]–[65]. Tryptophan, which can be produced by *Lactobacilli* spp., *Bifidobacterium* spp., *Clostridium sporogenes,* and *Clostridium bartettii*, is a precursor of dopamine and is a

metabolite of the kynurenine pathway [63], [64]. This pathway depends on IDO (found in all tissues and yeast) and TDO (found in the liver). The kynurenine pathway is affected by inflammation because increased activity of two enzymes can deplete serotonin and cause depression. The end products of tryptophan metabolism are kynurenine, kynurenic acid, xanthurenic acid, and quinolinic. Kynurenine and kynurenic acid have anti-inflammatory properties by decreasing INF-γ activity, whereas quinolinic acid is produced by activating microglia and macrophages [63], [65]. A study attempted to explain why ADHD patients have lower levels of serotonin. It revealed a decrease in tryptophan transport capacity into the brain. Another study discovered decreased function and expression of serotonin selective reuptake transporter (SERT) in the intestine, which leads to an increase in serotonin concentration. However, they cannot cross the BBB, so a lower concentration is available in the brain [65].

Pyridoxal phosphate (PLP), an active form of vitamin B6, is an essential coenzyme for neurotransmitter metabolism. PLP deficiency was observed in ADHD, implying vitamin B6 deficiency [64], [65].

Changes in the microbial environment in the gut increase intestinal permeability, allowing bacteria to migrate in systematic circulation. That increases systemic inflammation, and inflammatory mediators can cross the BBB and enter the brain, activating microglial cells. ADHD children have higher levels of pro-inflammatory cytokines such as INF-γ and IL-16 [63], [65]. Children with atopic diseases, such as atopic dermatitis, allergic rhinitis, and autoimmune diseases, have a higher risk of developing ADHD later in life than non-atopic children. High levels of circulating pro-inflammatory cytokines such as IL-13, IL-16, and TNF-α have been linked to ADHD symptoms [64], [65]. Allergies and skin inflammation are accompanied by an increase in the production of pro-inflammatory cytokines such as IL-6, IL-1, TNF-α, and IL-8. *Faecalbacteria* spp. were found in low abundance in Atopic diseases. Anti-inflammatory properties distinguish these bacteria. Because atopic disease patients have a high level of pro-inflammatory cytokines and a low abundance of *Feacalbacteria* spp., these abnormalities are thought to contribute to the pathogenesis of ADHD [11], [65]. *Dialister* spp. is linked to altered temperament and impulsive behavior in ADHD children. In a review, these children had elevated levels of IL-6 and IL-1. A study discovered that a low abundance of *Dialister* spp. is associated with a lower level of intense pleasure and a high level of IL-6. This is explained by the fact that a high level of IL-6 increases neurological inflammation, decreasing cortical volume and altering behavior [65].

Stress or pro-inflammatory mediators stimulate the HPA axis, releasing cortisol from the adrenal gland because of this axis. In stressed children with ADHD of the combined type,

salivary cortisol levels have been observed (hyperactivity and impulsivity). On the other hand, low cortisol levels in adults with ADHD after stressful exams [65].

BDNF is a neurotrophic factor that is required for neuronal survival. Gut microbiotas increase neuroplasticity by inducing the production of BDNF through forming SCFAs. *Bifidobacterium longum* was found to normalize BNDF level changes. Plasma BDNF was found to be altered in ADHD patients, implying a role in the pathogenesis of ADHD [63], [65].

Oxidative stress causes neuronal damage and abnormal neurotransmission, both of which are linked to ADHD [63]. In ADHD patients, the mitochondrial function of dopaminergic neurons has been altered. Changes in mitochondrial function result in uncontrolled production of reactive oxygen species, which activates microglia and causes the release of pro-inflammatory cytokines and members of the nucleotide-binding and oligomerization domain (NOD)-like receptor family [11].

Polyunsaturated fatty acids (PUFAs) are essential components of neuronal membranes, neurotransmission, and receptor functions. Intrauterine PUFA deficiency alters cognitive and attentive abilities. Omega-3 PUFAs can boost macrophages while decreasing IL-1 levels. High omega-6 consumption results in the development of low-grade systematic inflammation. As a result, omega-6 / omega-3 PUFAs with a low ratio should be sought after. Omega-3 influences the levels of neurotrophins, particularly BDNF. Low omega-3 intake has been linked to various inflammatory-related psychiatric disorders [63], [65].

ADHD patients have sleep disturbances and a significantly delayed circadian phase. The precise cause is unknown, but it is thought to be related to delayed melatonin secretion. Melatonin secretion is regulated by the central circadian clock in the CNS. Sleep disruption was suspected to be caused by a variation in the CLOCK gene [11].

As previously stated, the development of gut bacteria begins during the perinatal period and continues throughout human development. The mode of delivery has an impact on the bacterial environment in the gut. Maternal stress during pregnancy influences neurodevelopment, increasing the risk of ADHD development [63]. Furthermore, maternal stress and paracetamol use during pregnancy raise the risk of ADHD development [64]. *Lactobacillus* and *Bifidobacterium* spp. can normalize corticosterone release and modulate colonic dysfunction, suggesting that bacteria can help restore HPA axis balance. Maternal infection was linked to immune activation and changes in gut microbiota, which has been linked to ADHD. Furthermore, maternal obesity and metabolic diseases such as diabetes and hypertension influence infant behavior. Breast-feeding affects gut bacteria, which in turn affects behavior. Obesity is also linked to ADHD because it increases a low-grade

inflammatory state, which causes behavioral and cognitive changes. Chronic deficiencies of certain elements, such as zinc, iron, magnesium, and iodine, as well as insufficient dietary consumption, have been linked to the development of ADHD. Because of its anti-inflammatory and antioxidant properties, polyphenolic extract from pine bark has been shown to reduce hyperactivity in ADHD children [63]. A study was conducted on 871 European newborns who received antibiotics during their first year of life, and they also measured IQ and reading tests as well as examined the possibility of ADHD using the Conners Rating Scale-Revised (CRS-R). The results revealed poor reading ability and high CRS-R scores. Because this was not an RCT, the data must be interpreted cautiously [65].

The investigation showed a high abundance of *Firmicutes, Bacteroidetes, Proteobacteria, Odoribacter, Enterococcus, Sutterella,* and *Actinobacteria* in ADHD children. On the other hand, the genus *Bifidobacterium* and *Bacteroidacea* and *Neisseriaceae* families were dominant in adolescents with ADHD. While the genus *Faecalibacterium* was observed to be decreased in ADHD patients. At the species level, high abundance of *Bacteroides caccae, Odoribacter splanchnic, Paraprevotella xylaniphila,* and *Veillonella parvula* in ADHD patients [11], [64].

In ADHD patients, a high concentration of cyclohexadienyl dehydratase (CDT) enzyme has been linked to a high abundance of *Bifidobacterium*. CDT is an essential enzyme in synthesizing phenylalanine, a precursor to dopamine and noradrenaline. Interesting, *Bacteroides* spp. was found to have a positive relationship with hyperactivity and impulsivity in ADHD patients. Continuing research has revealed an increase in *B. uniformis*, *B. ovatus*, and a decrease in *B. coprocola* spp. in ADHD children [11], [64], [65].

5.7. Epilepsy

Epilepsy is a neurological condition characterized by recurrent, unprovoked seizures. These seizures are brief bursts of abnormally high electrical activity. In addition, glial cells play an essential role in the homeostasis of ions as well as the neurotransmitters, especially glutamate and GABA. Epilepsy can be caused by various factors, including CNS infection, cerebral malformation, trauma, stroke, and sometimes for no apparent reason.

The balance of GABA and glutamate maintains a balance between excitation and inhibition. This balance is disrupted when glutamatergic neurotransmission is stimulated while GABA is suppressed. Seizures are sometimes associated with schizophrenia and autism.

According to one study, changes in emotional behavior in childhood were observed because of gut bacteria disruption [66].

Gut bacteria play a role in epilepsy and epileptogenesis by activating the immune system, which produces a pro-excitatory effect of peripheral inflammation and influences neurotransmitter production (especially serotonin and GABA). SFAs influence the balance of excitation and inhibition. Furthermore, gut bacteria promote endocannabinoid system (ECS) dysregulation, increase intestinal permeability, and modulate the HPA axis and neural pathway [66].

Higher levels of proinflammatory cytokines, such as interleukin 6 (IL-6) and interferon, have been found in the peripheral blood of epileptic patients, indicating a role of immune factors in the pathogenesis of epilepsy. Other studies discovered that the level of IL-17A in epilepsy patients' cerebrospinal fluid (CSF) or peripheral blood was significantly elevated and that it was related to seizure frequency and severity. This cytokine is produced by lymphocyte helper T (Th) cell subsets. Th17 cells have been shown to participate in inflammatory responses in various autoimmune diseases affecting the nervous system, highlighting the importance of Th17/IL-17A signaling in these diseases. *Bacteroides*, for example, can modulate Th17 [67].

Neuro-inflammation causes cell death, which contributes to seizure occurrence. Furthermore, epileptic seizures activate immune cells, microglia, and the production of pro-inflammatory cytokines, all of which lead to the development of epilepsy. GABA, 5-HT, and dopamine are neurotransmitters, and neuropeptides (substance P, calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal polypeptide) interact with microbiota. Epilepsy is caused by the same neurotransmitters and neuropeptides, as well as Na+, Ca2+, and K+ channels. GABA can cross the BBB via its transporter and can also indirectly affect the enteric nervous system and vagus nerve by modulating receptor expression [66]. *A.mucinophilia* and *Parabacteroides* protect against seizures by modulating neurotransmitter levels in the hippocampus, including GABA and glutamate. Dysbiosis affects GABA levels and alters them, causing seizures to worsen [68].

SCFAs influence the brain by modulating metabolism and immunity either indirectly or directly via G-protein-coupled receptors (SCFA receptors, FFAR3 and HCAR2) or epigenetically via histone deacetylases. Histone modifications are critical for neurobiological process regulation, and disruption of this process contributes to the pathogenesis of epilepsy and epileptogenesis [66].

Stress causes cortisol release by activating the HPA axis. The pathogenesis of epilepsy is influenced by changes in stress response and HPA-related hormones [66].

The endocannabinoid system (ESC) is a crucial component of the neuro-modulatory pathway. Cannabinoid receptors (for example, CB1Rs and CB2Rs), endogenous cannabinoids (endocannabinoids), and the enzymes responsible for their synthesis and degradation are all part of the ECS. This system is essential for CNS development and synaptic plasticity and responds to endogenous and environmental insults. CB1Rs are found primarily in the brain, whereas CB2Rs are found in the gut, neurons, epithelial cells, and immune cells. LPS has been linked to ESC dysregulation in macrophages because it induces the production of endogenous ligands for cannabinoid receptors, such as anandamide, in adipose tissue and macrophages, particularly in chronic inflammation in visceral fat, hyperglycemia, and insulin resistance. Depending on the mechanism mentioned above, some studies suggest that LPS-induced peripheral inflammation increases seizure susceptibility [66].

Many studies have found that antibiotics such as penicillin, fourth-generation cephalosporins, imipenem, and ciprofloxacin can cause epilepsy, especially in patients with renal dysfunction, brain lesion, or epilepsy. In contrast, a retrospective study found that antibiotics benefit seizures because they modulate gut bacteria. This study only included six patients and used azithromycin, clindamycin, amoxicillin/clavulanic acid, and piperacillin/tazobactam [66], [68], [69]. Penicillin's -lactam ring has non-competitive inhibitory properties against GABA-A receptors. Quinolones can bind to benzodiazepine receptors in the GABA complex. Furthermore, quinolones and cephalosporins have an agonist effect on NMDA receptors, contributing to seizure occurrence. Carbapenem, the most used drug to induce seizures, can cross the BBB and interfere with some antiepileptic drugs, including valproic acid. On the other hand, some antibiotics, such as Rapamycin, an mTOR inhibitor, have antiepileptic properties [69]. According to one study, children with an infection and require hospitalization have a 78% increased risk of epilepsy. Furthermore, infected infants with group B *Streptococcus* have been linked to being hospitalized and diagnosed with epilepsy or other neurological conditions during childhood [69].

The ketogenic diet (KD) is a non-drug treatment option for refractory epilepsy. It consists of a high-fat, adequate-protein, and low-carbohydrate diet. It is also supplemented with vitamins and minerals. That means, ketones, which are formed by KD, are used as an alternative source of energy substrate for ATP production in cells, including brain cells. The altered metabolic profile reduces neuronal excitability and the number of seizures. The precise mechanism is unknown, but it is assumed that this effect is achieved by inducing GABA-mediated inhibition, direct inhibitory actions of polyunsaturated fatty acids on ion channels, increased ATP levels that are converted to adenosine, or increased mitochondrial biogenesis

and decreased oxidative stress [66], [68]–[72]. Glucose is the typical substrate for neurons under normal conditions. Glucose transporters are present in the brain capillary endothelial layer to facilitate its diffusion across BBB. The glucose metabolism generates the required energy for seizure activity. In contrast, in KD patients, generated energy from blood glucose is low, so the brain must use KB for energy. This anaerobic metabolism slows the availability of energy, which reduces seizures. Chronic ketosis may play a role in the anticonvulsant properties of KD, as it has been demonstrated that chronic ketosis increases brain energy reserve via synaptic stabilization and reduction in excitability [71]. KD reduces aspartate concentration. Aspartates inhibit glutamate decarboxylase, an enzyme that aids in converting glutamate to glutamine in astrocytes. Because of the low aspartate concentration, KD activates glutamate decarboxylase, resulting in GABA synthesis [71], [72]. KD compliance is low due to its unpleasant and restrictive features. It also causes dehydration, hypoglycemia, lethargy, metabolic acidosis, and gastrointestinal symptoms like constipation, diarrhea, vomiting, and abdominal pain. It reduces weight while increasing LDL and total cholesterol [71], [72]. During KD, a low abundance of *Actinobacteria, proteobacteria,* and *Bifidobacterium* and a high abundance of *Akkermansia muciniphila, Parabacteroides* spp., *Prevotella, Bacteroides,* and *Bifidobacterium* have been observed [68], [69], [71], [72]. *Bacteroides* can digest and metabolize high-fat foods, and, in turn, this regulates the production of IL-6 and IL-7, which are secreted by dendritic cells. Furthermore, *Prevotella* can produce a large amount of SCFAs, which modulate congenital functions [68]. KD effectively treats Glucose Transporter 1 Deficiency Syndrome (GLUT1 DS), a genetic disorder characterized by seizures. In one study, patients with GLUT1 DS had an increased abundance of *Desulfovibrio* spp. During treatment with KD. *Desulfovibrio* spp. is a bacterium that reduces sulfate and is involved in inflammation. This alteration reduces the abundance of *Bifidobacteria*. *Bacteroides* were also linked to changes in the functional profile of gut bacteria during KD [70], [71].

The gut bacteria influence antiepileptic drugs. The gut bacteria can metabolize Zonisamide, an anticonvulsant drug, into 2-sulfamoylacetylphenol. Under anaerobic conditions, *Clostridium sporogenes* and *Bifidobacterium bifidum* can achieve this metabolic process [68], [70]. Anticonvulsant drug clonazepam was reported to be metabolized by intestinal bacteria, leading to drug toxicity [69]. Lamotrigine may inhibit *E. coli* growth [68].

High abundance of *Firmicutes,* including *Roseburia, Coprococcus, Ruminococcus,* and *Coprobacillus,* and decreased abundance of *Bacteroides* have been observed in refractory epileptic patients. A relative increase in abundance of *Methanobrevibacter, Fusobacterium, Neisseria,* and *Akkermansia* was observed in refractory epilepsy than in drug-sensitive epilepsy

patients. Similar observations were in infants with refractory epilepsy, as there was a high abundance of *Firmicutes* and *Proteobacteria* while a decreased abundance of *Bacteroidetes, Prevotella, Bifidobacterium,* and *Actinobacteria*. *Cronbacter* was highly observed in epileptic infants but not observed in healthy infants [66], [68]–[70].

One of the possible used probiotics in epilepsy: is *Saccharomyces boulardii*, which is supposed to reduce the seizure through inhibition of rotavirus structural protein 4 or to suppress the inflammatory response. Rotavirus structural protein 4 is enterotoxin, which increases reactive oxygen species and white matter injurty. Another probiotic is a cocktail of *Lactobacillus acidophilus, L. plantarum, L. casei, L. helveticus, L. brevis, Bifidobacterium lactis,* and *Streptococcus salivarius* [68], [69].

6. Altered Gut- Brain axis in autoimmune diseases

6.1. Irritable bowel syndrome

Irritable bowel syndrome's pathophysiology mechanism is frequently cited as being uncertain. A review article offers a helpful justification, however. Since this condition may be brought on by altered serotonin metabolism, visceral hypersensitivity, persistent infection, low-grade mucosal inflammation, altered post-infection alterations, altered microbiota, and genetic factors (due to mutations of SCN5A) [73]. The four subtypes of irritable bowel syndrome (IBS) include unclassified IBS, IBS with mixed bowel habits (IBS-M), IBS with diarrhea (IBS-D), and IBS with constipation (IBS-C). According to Rome's IV criteria, an evaluation is conducted to determine the presence of irritable bowel syndrome. More women than men are vulnerable to the event. The patient consistently experiences irregular bowel movements, digestive issues such as dyspepsia, and excruciating abdominal discomfort. It is connected to a mental illness like anxiety or depression [4].

Man cannot reject the function of fungal dysbiosis in visceral hypersensitivity, but it has been found that the lack of *methanobacteriales* and enrichment with *Bacteroides* enterotypes has a favorable influence on the severity of IBS [4]. Dysbiosis stimulates the production of the cytokines IL-6, TNF-α, and IL-1 and activates the gut immune system. However, the main reason for immune response change remains unknown. Stress is thought to increase the release of pro-inflammatory molecules like IL-6 and IL-8, which activates the hypothalamus, pituitary, and adrenal glands (HPA) and causes the release of hormones like cortisol adrenocorticotropic

hormone, and corticotrophin-releasing factor (CRF), which affects gut homeostasis. Additionally, it has been noted that variations in serotonin metabolism affect gut motility and have an impact on the pattern of IBS, as seen by the high serotonin levels in an IBS-D patient. On the other hand, low serotonin levels in an IBS-C patient [4].

The diet also plays a role in the pathophysiology of IBS since it affects the gut's motility, permeability, gut bacteria, visceral feeling, immune system, and neuroendocrine function. The ingestion of certain foods, such as gluten and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), is associated with worsening IBS symptoms. Gluten is thought to have an impact on intestinal permeability and neuron activity. In addition, it has been demonstrated that IBS patients who consume FODMAPs experience bloating and pain in their abdomens. FODMAPs cause bloating because they are short-chain carbohydrates that can be digested fast and create methane and hydrogen gases, which drive gut motility and GI distention [4].

Visceral hypersensitivity is the term for increased pain perception in the visceral organs due to exposure to mental, physical, and emotional stress. Visceral hypersensitivity in IBS has not yet been fully explained [4]

Bacteria and other small creatures, including viruses, fungi, and archaea, play a crucial role in the gut microbiome. *Firmicutes* (64 %), *Bacteroidetes* (23 %), *Proteobacteria* (8 %), and *Actinobacteria* (3 %) are the groups that make up most of the environment in the gut. Methanogens and halophilic groups are subdivided into many *Archaea* species found in the gut. *Methanomethylophilus alvus*, *Methanobrevibacter simithii*, *M.stadtmane*, and *Candidatus.* "*Methanomassiliicoccus intestinalis*" are examples of methanogens [4].

The SCFAs can alter the intestinal motility and mucosal permeability that the gut bacteria can create, including acetate, propionate, and butyrate. It has been shown that butyrate-producing bacteria exist in IBS-D and IBS-M patients and play a part in enhancing the function of the intestinal barrier. Sulfate-reducing bacteria can remove excess hydrogen and convert it to methane, which is associated with diminishing the anti-inflammatory action in the colon and methane-producing bacteria from the *Archaea* [4].

According to Studies, decreasing levels of *Bifidobacterium*, *Faecalibacterium*, *Erysipelotrichaceae*, and *methanogens* are associated with altered gut hemostasis, as is an increase in *Firmicutes* like *Lactobacillus* and *Ruminococcus* and *Proteobacteria* such the phylum *villanelle*. When eating high-salt foods, halophilic archaea, including *Halorubrum koreense*, *Halorubrum alimentarium*, *Halorubrum saccharovorum*, and *Halococcus morrhuae*, are found in the gut [4].

According to many studies on bacterial dysbiosis, this condition alters the immune system, affects the number of *Firmicutes* and *Bacteroidetes*, and plays a role in post-infection, which explains why IBS develops into a chronic condition. Patients with *Clostridium difficile* infection who developed IBS, particularly mixed-IBS, six months or more after the infection are an example of this. In addition to the chronic infection, it has been noted that CD8 T lymphocyte impairment coexists with dysbiosis during the acute phase of giardiasis [4].

It has been hypothesized that in the IBS microbiome, some bacterial species like *Enterobacteriaceae* reduce the number of other bacterial species like *Lactobacillus* and *Bifidobacterium*. Additionally, bacteriocins produced by *Lactobacillus* and *Bifidobacterium* can fight diseases like *Listeria monocytogenes* and the *Salmonella* genus. Dendritic cells' surface protein CD209 interacts with *Lactobacillus* and *Bifidobacterium* to modify the gut immune system [74].

By treating IBS, we may leverage the microbiota to our advantage. The usage of probiotics like *Bifidobacterium* and *Lactobacillus* strains is one of the therapy options. *B.infantis* alone cannot alleviate IBS symptoms like bloating and pain, but it can when used in conjunction with probiotics. Despite the probiotics' remarkable results, it is still unclear how they function. They might gain from individualized or tailored probiotic therapy in the future. Prebiotics are a great alternative to probiotics for treating IBS because of the short shelf life of probiotics. Lactulose, one of the popular synthetic prebiotics, has a laxative impact, improves water retention in stools, and raises gut flora. Prebiotics that are taken includes fructo-oligosaccharides (FOS), soybean oligosaccharides, galacto-oligosaccharides (GOS), isomaltose-oligosaccharides, Xylo-oligosaccharides, and trans galactic-oligosaccharides (TGOS). Polysaccharide prebiotics includes fructan, inulin, cellulose, hemicellulose, reflux starch, and pectin. Prebiotics can be fermented by gut bacteria, which can also create SCFAs. For example, most *Bifidobacterium* and *Lactobacillus* can ferment FOS. SCFAs can bind to the GPR43, GPR41, and GPR109A G-protein coupled receptors, which control inflammation. Probiotics can modulate cholesterol production and lipid synthesis, as well as moderate dysbiosis and microbiota. The manipulation of microbiomes such as those of *Saccharomyces*, *Malassezia*, and *Candida* is one of the probiotics' emerging techniques since the fungal Hepatitis B, cystic fibrosis, inflammatory bowel conditions, and IBS all have a link to dysbiosis [74].

Symbiotic are another potential IBS therapeutic option. As synergism, probiotics and prebiotics are combined in food ingredients. Its effectiveness has not been established because there have not been many clinical trials. Non-adsorbable antibiotics are another way of treating

IBS. Rifaximin is the most well-known example of a non-absorbable antibiotic with a broad spectrum that slows the growth of both aerobic and anaerobic organisms. Rifaximin has shown to be effective in treating IBS patients with small intestine bacterial overgrowth (SIBO). Neomycin has also been noted to reduce IBS symptoms only when accompanied by *Clostridium difficile* infection or rapid bacterial resistance [4]. Another option for treating people with chronic loose and frequent feces, including IBS-D, is serum-derived bovine immunoglobulin (SBI), but only when used under medical supervision. More than 90% of it is protein, and more than 50% is immunoglobulin G (IgG). The gut microbiome was shown to have changed due to SBI, particularly in the *Burkholderiales* and *Firmicutes, Catanella* in the intestinal mucosa but not in the stool. Only the production of bile acid changed the intestinal permeability. IBS symptoms are significantly influenced by food. As short-chain carbohydrates like fructans, polyols, and galacto-oligosaccharides are poorly absorbed in the small intestine, a low-FODMAP diet is one dietary intervention for IBS. Low FODMAP diets have been demonstrated to diminish the production of pro-inflammatory cytokines and the amount of gut bacteria such as *Actinobacteria*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, even though they are beneficial for IBS. The effectiveness of the gluten-free diet in reducing IBS symptoms has been established. Fecal microbiota transplant is another option for treating IBS. To restore gut homeostasis, this procedure involves transferring a solution of fecal material from a healthy donor into the recipient's gut. This approach's effectiveness is being examined [4].

Future approaches to treating IBS include postbiotics, bacteriophage therapy, and stem cell-based "gut-on-a-chip." Modern technology is used to create stem cell-based "chips" that mimic the human gut lining using "organoids," which are induced pluripotent stem cells (iPSCs). Intestinal villi stem cells are created using iPSCs extracted from skin or blood samples. Microfluidic engineering and the Gut-on-a-Chip were integrated to stimulate the gut environment. However, it has been noted that there are specific alterations in bacteriophage diversity in a sick condition. Bacteriophages are used to restore gut homeostasis. The bacteriophage will be used to attack certain dysbiosis, according to strategy. The term "postbiotics" refers to elements that are not viable, such as parts of bacterial cell walls, enzymes, peptides like glutathione, and polysaccharides produced by living bacteria or released after their lysis. It offers better benefits than probiotics because of its safety profile and longer half-life. Utilizing CRISPR-Cas9 technology to alter the population of bacteria like *Methanobrevibacter smithii* and decrease methane production is another advancement in treating IBS. Alternately, the oral cavity can be treated with the specific targeted antimicrobial

peptide (STAMP) technology. To treat IBS, a man can utilize this technique to alter the habitat of the gut microorganisms. *Myovirus* bacteriophage T4 and Pseudomonas aeruginosa can produce contractile nanotubes. These nanotubes attach to the surface of bacterial cells, enclose themselves within the cell wall, and create an ionic flow that kills the bacteria [4].

6.2. Inflammatory bowel disease.

The two most prevalent clinical forms of inflammatory bowel illness are Crohn's disease and ulcerative colitis (IBD). Ulcerative colitis only affects the colon, whereas Crohn's disease can affect any digestive tract area. The histology of the intestinal epithelium and the immune system in the gut both play a role in the pathophysiology of inflammatory bowel disease. Microbiomes are another element that influences the onset of disease. One of the secretory cells, goblet cells, secrete mucus and antimicrobial peptides that influence the gut microbial population. The processes of fibrosis and wound healing involve stromal cells. Additionally, alpha-defensins, lysozyme, and secretory phospholipase A2 are secreted by Paneth cells. IgA is produced by plasma cells and is crucial for preserving the equilibrium of the gut microbiota and preventing dysbiosis [75].

It was shown that the colon, where the illness activity increased, had a higher bacterial population. Inflammatory bowel illness and the microbiome are related, as is the genetic variation in the immune cells in the gut. The pathophysiology of this illness is greatly influenced by the genes nucleotide oligomerization domain 2 (*NOD2*), autophagy-related 16-like 1 (*ATG16L1*), caspase recruitment domain-containing protein 9 (*CARD9*), and C-type lectin domain family seven-member A (*CLEC7A*). The intestinal epithelial cell, which protects against dysbiosis and has intracellular pattern recognition receptors, interacts with peptidoglycan in both gram-positive and gram-negative bacteria. *NOD2* is present in this cell. *The NOD2 mutation causes IL-10 levels to drop and mucosa-associated bacterial populations to rise.* Low numbers of *Faecalibacterium* species and large numbers of *Escherichia* species are associated with the *NOD2* mutation. The autophagy process, which is in charge of eliminating hazardous bacteria since they can be invasive to the bacterium, is regulated by *ATG16L1*. Antigen presentation and bacterial clarity are reduced due to the *ATG16L1* mutation. In the event of an infection with *Bacteroides fragilis*, the mutation can impede the formation of regulatory T-lymphocytes. As they can identify the elements of the fungal cell wall, *CARD9* and *CLEC7A* are in charge of fungus clarity. Additionally, *CARD9* is essential in creating

inflammatory mediators during bacterial and viral infections. The prevalence of invasive Candida species infections in the central nervous system and digestive tract is increased by *CARD9* deficiency. When *CARD9* is lost, TH17 cells become feeble, which interferes with the integrity of the mucosal barrier [76].

The immune response is altered, and the disease worsens when the equilibrium between Th17 and Treg is upset. IBD is correlated with an increase in *Ruminococcus gnavus* aa and a decrease in *Bifidobacterium adolescentis, Dialister invisus,* and *Faecalibacterium prausnitzii*, among other bacterial species [77].

The regulatory T cells in the colon are controlled by SCFAs, which are thought to be the energy supply for colonic epithelial cells. The butyrate production is decreased due to the decline in the population of bacteria such as *Bacteroisetes* and *Clostridium* clusters IV and XIVa, including *F. prausnitizii*. Sulfate-reducing bacteria are linked to IBD because hydrogen sulfide can prevent colonocytes from using butyrate. Low levels of the secondary bile acids lithocholic, deoxycholate, vitamin B5, and vitamin B3 are found in IBD patients. The synthesis of sphingolipids and carboxamide acids is one of the *B weak* defense mechanisms iKiller T (iNKT) cell agonists can inactivate the iNKT cell due to structural similarities to invariant nature [76]. *F. prausnitzii* has been identified as a crucial component in IBD after its low concentration was discovered in the stool of individuals experiencing a relapse of Crohn's disease. *F. prausnitzii* can create metabolites that stop mucosal cells from producing IL-8 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) from activating. Additionally, these bacteria produce salicylic acid and butyrate, which can boost the serum's low levels of IL-12 and IFN-α [19]. *Mycobacterium avium subsp, para-tuberculosis (MAP),* whose existence is substantiated by the discovery of antibodies and reactive T-cells against MAP in patients with Crohn's disease, is another bacterial species that may be involved in IBD. In many IBD instances, *Clostridium* difficile was discovered [77].

The fungal infection increases in Crohn's disease while decreases in ulcerative colitis. It was reported that *Saccharomyces cerevisiae* decreased, and *Candida albicans, Candida tropicalis, Clavispora Lusitania, Cyberlindnera jadinii,* and *Kluyveromyces marxianus* increased. However, *Malassezia restricta* is found on the skin but also in the intestinal mucosa of patients with Crohn´s disease. Also, it has been noticed that there are Caudovirales bacteriophages in the faecal culture of patients with IBD [76].

Breastfeeding prevents the onset of IBD because it contains *Bifidobacteria, Leuconostoc mesenteroides, Lactobacillus rhamnosus, Lactobacillus gasseri,* and *Lactobacillus lactis*. This microbiota maintains the mucosal epithelial barrier, boosts immunological response, and

lowers the risk of infection. Additionally, because breast milk oligosaccharides have a prebiotic effect, they can prevent several dysbiosis from adhering to epithelial cells, including *Salmonella fyris, Vibrio cholera*, and *E. coli*. Crohn's disease is negatively impacted by smoking, while ulcerative colitis is protected. Following smoking cessation, it has been noted that *Bifidobacterium* species are more prevalent in non-smokers than in smokers [76].

Prebiotics, such as carbohydrates, which treat inflammatory bowel disease (IBD), promote microbes' growth by lowering the colon's pH, which is a favored habitat for *Bifidobacteria*, *Lactobacilli*, and non-pathogenic *E. coli*. Foods made from germinated barley are another prebiotic (GBF). It has hemicellulose and glutamine, both beneficial for IBD patients. They also promote the growth of Bifidobacterium and Eubacterium while lowering CRP levels. Supplementing with fructo-oligosaccharides (FOS) and inulin are more prebiotics that enhances gut microbiomes [77].

The use of probiotics, which enhance intestinal barrier function and the bacterial habitat in the gut, is one of the possible treatments. For instance, the probiotic supplement VSL#3 contains a combination of four different *Lactobacillus* species strains, three different *Bifidobacterium* species strains, and *Streptococcus salivarius.* A formulation including *Lactobacillus* GC, inulin, *Bifidobacteria*, and FOS is an example of a synbiotic, which combines probiotics with prebiotics. This composition can boost IgA and IL-10 production and reduce colonic carcinogenesis. Patients with mild to severe ulcerative colitis also experienced anti-inflammatory benefits from combining the *Yakult* strain and galacto-oligosaccharides [77].

Despite the absence of supporting data, antibiotics like ciprofloxacin and metronidazole are used to treat IBD. Rifaximin reduces the signs and symptoms of sickness but has no impact on curing it. Clinical efficacy for antibiotic combinations, including metronidazole, amoxicillin, doxycycline, and vancomycin, is good [21]. Although it showed promising outcomes in treating *Clostridium difficile* infection, faecal microbiome transport (FMT) is one therapy approach without adequate data [76].

IBD is treated with traditional Chinese medicines such as pulsatilla decoction, chai hu peony soup, and wumei pill decoction. Due to its immunosuppressive properties and ability to coexist with gut microorganisms, the polysaccharide of Chinese H. acts serves as adjuvant therapy in the treatment of IBD; nevertheless, it has a far less significant impact on the restoration of gut bacteria. To be employed in treating immunological disorder diseases, it also plays a part in regulating Th1 and Th2 [20]. Genetically modified strains that supply tailored microbiomes, next-generation FMT, and live biotherapeutics are the future of medicine [78].

6.2.1. What are the similarities between inflammatory bowel disease and Parkinson´s disease?

After discovering a 20–90% increase in the likelihood of developing PD in individuals with IBD, the similarities between both conditions must be kept in mind. Age is a crucial determinant when predicting the onset of PD in IBD patients. In IBD patients older than 60, the risk of PD is said to increase by 32%; however, a different study showed that PD develops remarkably in IBD patients younger than 60. As drug-induced parkinsonism has been hypothesized to be another factor that prevents PD from developing in IBD patients, it cannot be determined that age is the primary cause of PD development in these patients. Antiemetics, prokinetics, and antipsychotic drugs, among others, can hasten the onset of PD when used to treat IBD. These drugs inhibit the dopamine receptor. Smoking is a confusing risk factor for IBD since it protects against parkinsonism and ulcerative colitis (UC) yet is detrimental to Crohn's disease (CD). An anti-tumor necrosis factor (TNF) medication or amino salicylate treatment for IBD demonstrated a reduction in the emergence of PD [79].

It was discovered that PD and IBD share several genomic areas. *MROH3P, HLA, CCNY, LRRK2, MAPT, SYMPK,* and *RSPH6A* are the regions that overlap with CD, and *GUCY1A3, HLA, BTNL2,* and *TRIM10* are the regions that overlap with UC. Leucine-rich repeat kinase 2 (LRRK2) is an intriguing link between two diseases because it was discovered that the pathogenic mutation of this gene in both diseases increases LRRK2 kinase activity. This finding led to the developing of an LRRK2 kinase inhibitor drug to treat PD, though its potential for use in treating IBD is still unknown. Due to its high expression in monocytes and dendritic cells, LRRK2 is also present in peripheral immune cells and is involved in the immunological response [79].

As is well known, both disorders' pathophysiology is significantly influenced by disruptions in the brain-gut axis. More research was needed even though it has been hypothesized that chronic intestinal inflammation accelerates the buildup of α-synuclein in the gut, which travels to the brain via systematic circulation, and that Lewy bodies are found in the gut of IBD patients over 20 years before they are diagnosed with PD. Significant calprotectin levels in PD patients' stools suggest that this condition could be predicted in IBD patients [79].

6.3. Multiple Sclerosis.

Multiple Sclerosis (MS) is a neurodegenerative disease that results in significant disability. It is distinguished by perivenular inflammatory lesions that result in demyelinating plaque formation. T-lymphocytes are responsible for inflammation. Considering the primary immune response consists of B-cells, Plasma cells, and CD8+ T-cells. This inflammation damages oligodendrocytes and demyelinates nerves, leaving them unrepaired [80].

The gut-brain axis plays a complex role in MS because the CNS regulates gut function through a dense innervation system and local immune response. Pro-inflammatory cytokines, neuropeptides such as cholecystokinin (CCK) and leptin, and neurotransmitters are used by intestinal immune cells. The microbiota influences the immune response by influencing immune cells in gut-associated lymphatic tissue (GALT). Toll-like receptors recognize LP, which is present in the outer membrane of many gut bacteria species, and this is what the immune uses to identify the bacteria. T-cell receptors are expressed by mucosa-associated invariant T (MAIT) cells, which also produce pro-inflammatory mediators such as interleukin 17 (IL-17) and interferon-gamma (IFN-γ), granzyme B, and tumor necrosis factor-alpha (TNF-α) [81].

SCFAs inhibit histone deacetylase (HDAC) activity in Treg and microglia cells. SCFAs also stimulate dendritic cells to produce anti-inflammatory mediators like retinoic acid and transforming growth factor (TGF-β). Tryptophan metabolites activate astrocytes and induce the Th17 pro-inflammatory phenotype. Dysbiosis causes tight junction dysfunction and alters intestinal permeability. In MS, intestinal barrier disruption is associated with elevated levels of LPS. Chronic low-grade inflammation and endotoxemia are caused by LPS-mediated signaling in the lamina propria. A low level of SCFAs caused by dysbiosis compromises the intestinal barrier, allowing inflammatory mediators to enter the brain and stimulate microglia and astrocytes in the CNS [9], [81]. Treg cells are a subset of CD4+ helper T cells that are in charge of immune balance. SCFAs increase Treg cell perforation and the anti-inflammatory cytokine IL-10 [9].

Sphingolipids produced by *Bacteroides fragilis* activate invariant nature killer (iNKT) cells. MS has been linked to a decrease in iNKT cells, a distinct subset of T cells. Many bacteria, including *Prevotella copri, Bacteroides vulgatus, Lactobacillus casei, Sphingomonas paucimobilis, S. yanoikuyae, Rothia dentocariosa,* and *Arthrobacter*, have been reported to produce iNKT cell ligands [9].

Gut bacteria can boost regulatory Th2 cells and inflammatory Th1 and Th17 cells. Intestinal bacteria have been found to stimulate the interaction of T-cell C-C chemokine receptor type 9 (CCR9) and its ligand chemokine (CCL25). This reaction is essential in T-cell development. CCR9 activity was found to be low in relapsing-remitting MS (RR-MS) [82].

There is a high abundance of *Firmicutes*, *Streptococcus mitis*, and *Streptococcus oralis* and a low abundance of *Bacteroidetes* and *Prevotella* in MS patients. *Prevotella* is responsible for the production of anti-inflammatory metabolites propionate. The low abundance of *Prevotella* was related to the expansion of Th17 cells and disease activity in RR-MS. It was noticed that there was a low abundance of the genus *Clostridium* (*Clostridia* cluster XIV and IV) and *Adlercreutzia* in patients with RR-MS. *Adlercreutzia* influences immune response and phytoestrogen metabolism. Phytoestrogens are products execrated from herbs. Its chemical structure and biological activity are like estrogen. In turn, the level of phytoestrogen is reduced and cannot fight oxidative stress and inflammatory cytokines, such as interleukin-6 and chemo-attracting proteins-1, which are elevated in RR-MS patients. A study showed a high abundance of *Methanobrevibacter* and *Akkermansia*, especially *Akkermansia muciniphila*, in MS patients. *Methanobrevibacter* contributes to inflammation by recruiting inflammatory and dendritic cells. In addition, *Akkermansia* damages the intestinal barrier and increases immune cell exposure to microbial antigens by degrading mucin and converting it into short-chain fatty acids, which can mediate immune-regulatory effects [9], [82]. In contrast, it was discovered that a high abundance of *Akkermansia* is associated with lower disability in MS, proving that *Akkermansia* has a beneficial effect not only in MS but also in other diseases [83], [84]. In RR-MS patients, a high abundance of *Anaerostipes*, *Faecalibacterium*, *Pseudomonas*, *Mycoplasma*, *Haemophilus*, *Blautia*, and *Dorea* was found [85]. A high abundance of *Desulfovibrionaceae* and a low abundance of *Lachnospiraceae* and *Ruminococcaceae* were observed in pediatric MS patients [9], [85], [86]. A low abundance of *Butyricimonas* was observed in MS patients, which produce butyrate. Butyrate has an anti-inflammatory and direct effect on oligodendrocytes, which fight demyelination. A low propionate level in serum of MS patients, which *Butyricimonas* produced, was reported [86], [87]. *Acinetobacter* species, rare in healthy humans, were observed in MS patients. In addition, a low abundance of *Parabacteroides* was also reported in MS patients [88].

Obesity is a risk factor for MS development, particularly in children and adolescents. Obese patients, like MS patients, had a high abundance of *Firmicutes* and *Actinobacteria*. *Bacteroidetes* were found in low abundance in obese MS patients. These bacteria produce SFAs, which are anti-inflammatory. Obesity and the level of 25-hydroxyvitamin D3, inactive

storage of vitamin D, have been linked, as low levels of these metabolites have been linked to MS development. Another factor is a lack of vitamin D. Vitamin D is an immunomodulator that plays a vital role in the immune response. Vitamin D inhibits IFN- γ production, maintains the gut environment, is a potent antioxidant, and promotes brain development by regulating neurotrophic factors. Vitamin D has been shown to promote Treg differentiation [82], [86].

MS treatment options are diverse. One is using antibiotics to modify the gut environment, such as minocycline. Another treatment option for MS is phage therapy. Phages are bacteria-specific viruses that target specific bacteria species while leaving other species alone. Oral admiration is safe because it can pass through the GALT and the systemic circulation. In this disease, vitamin D supplementation is a vital therapeutic option [85], [89].

One probiotic, a combination of *Lactobacillus, Streptococcus,* and *Bifidobacterium*, demonstrated significant improvement in MS patients. As part of a probiotic mixture, *L. reuteri* can improve CNS autoimmunity by inhibiting encephalitogenic T cells in the small intestine. Encephalitogenic T cell activation causes inflammatory damage, including demyelination and axonal loss [88]. *Prevotella histicola* has been identified as a potential immunomodulatory agent, as it can reduce Th1 and Th17 cells while increasing Treg and tolerogenic dendritic cells [89].

6.4. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune illness that causes pain, stiffness, inflammation, and swelling in the joints and can lead to significant joint destruction, loss of function, and disability. The disorder can last from months to a lifetime, and symptoms might improve or worsen over time. Anti-citrullinated protein antibodies (ACPAs), anticyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF) detection are required to forecast the beginning of rheumatoid arthritis [90], [91].

The altered immunological response is the initial step toward autoimmunity. The presence of autoantibodies and autoreactive T cells indicates immune system dysfunction. The most visible immune system modification in these patients is the improper development of autoreactive B cells; they are recognized long before the illness manifests itself. The most significant are RF and ACPAs, which identify various citrullinated proteins. Besides the increased autoantibody synthesis, pro-inflammatory cytokines are enhanced in the joint synovium of rheumatoid arthritis patients. The joints of RA patients are complex tissues,

including innate and adaptive immune cells as well as joint resident cells, such as synoviocytes and chondrocytes. Dendritic cells are usually observed in the rheumatoid synovium lymphocytic aggregates and peripheral arteries. MHC alleles are expressed by APCs, which destroy extracellular peptides and deliver them to CD4+ T cells, causing the release of pro-inflammatory cytokines, which activate B cells to make antibodies. A decrease in circulating regulatory T cells (Treg) function and an increase in T helper 17 (Th17) cells in plasma and synovial fluid TGF from macrophages and dendritic cells, as well as IL-1 β, 6, 21, and 23, promotes Th17 development while suppressing regulatory T cell differentiation, pushing T cell homeostasis toward inflammation [92], [93].

Citrullination (a Posttranslational modification (PTM) of arginine), carbamylation (a PTM of lysine), and malondialdehyde-acetaldehyde adducts are all recognized by RA autoantibodies (MAA). Citrullination, glycosylation, and carbamylation are involved in the pathogenesis of RA. Citrullination is mediated by peptidyl arginine deiminases (PAD) and modifies the tertiary structure of the modified protein, allowing neo-epitopes to be exposed. Carbamylation is a non-enzymatic PTM in which cyanate binds to the main amine of lysine and generates carbamyl groups, resulting in peptidyl-homocitrulline (anti-CarP). Anti-CarP antibodies have been found in both ACPA-negative and ACPA-positive pre-RA patients and those with developed RA. MAA is formed when lipid peroxidation by ROS produces highly reactive malondialdehyde and acetaldehyde molecules. This mechanism alters lysine residues to produce stable MAA. MAA levels were higher in patients with established RA, and MAA levels were linked to ACPA. Anti-MAA antibodies are found in more significant amounts in the RA joint than in the serum [92]–[94].

ACPA titers and epitope diversity rise, especially before arthritis develops. ACPAs are IgG, IgA, or IgM isotypes with altered glycosylation, increasing Fc-receptor and citrullinated antigen binding. ACPAs can cause bone loss by stimulating either macrophages or osteoclasts via immune complex formation and Fc-receptor interaction or by binding membrane citrullinated vimentin [92], [93].

Another mechanism must be considered: the production of neutrophil extracellular traps (NETs), also known as NETosis. The NETosis method includes the release of decondensed chromatin with bound proteins like histones and antimicrobial peptides after neutrophil lysis, generating traps for specific bacteria. The citrullination of nuclear proteins such as histones (particularly H2A, H3 and H4) by the PAD4 enzyme, which is highly expressed in neutrophils, is an essential step in NETosis. After performing their extracellular killing role, NETs are eliminated in healthy persons. NETs are cleared by extracellular DNAse I and macrophages,

which may engulf and digest NETs. Autoantibodies to citrullinated histones H4, H2A, and H2B are prevalent in RA patients, as well as incomplete clearance of NETs has also been observed in RA. Calcium cations are required for human PADs to fulfil their citrullinating activity. When human PADs are released into the calcium-rich extracellular space following a NETosis event, they are likely to have an abnormally enhanced citrullinating activity [93].

The mucosal immune system is thought to be the basis of RA autoimmunity. Autoimmune arthritis, which develops on its own, causes a rise in the formation of serum amyloid A (SAA) in the ileum. SAA activates dendritic cells in the lamina propria, promoting CD4+ T cell differentiation into Th17 cells. Furthermore, the gut flora can generate a large quantity of adenosine 51-triphosphate (ATP). ATP stimulates $CD70_{high}CD11c_{low}$ cells, which are found only in the lamina propria. This cell type can release IL-6, IL-23p19, and transforming-growth-factor-activating integrin -αV and -β8, which promote Th17 development. This process raises pro-inflammatory cytokines such as IL-21, IL-22, GM-CSF, and TNF- α. These pro-inflammatory mediators have an essential role in the pathophysiology of RA, particularly in pannus formation, osteoclastgenesis, and synovial neoangiogenesis. IL-17 and IL-22 may promote RANKL expression in human synovial fibroblasts, resulting in an imbalance of RANKL/OPG and increased osteoclast activity and bone degradation. Furthermore, IL-17 can stimulate the synthesis of vascular endothelial growth factor (VEGF) in rheumatoid fibroblast-like synoviocytes (FLS), leading to angiogenesis in rheumatoid synovium. In addition, IL-17 stimulates the expression of various pro-inflammatory cytokines (e.g., IL-1, TNF-α, and IL-6) as well as matrix-degrading enzymes (e.g., matrix metalloproteinase (MMP)-1, -2, -9, and -13) in synovial tissue, synovial fibroblasts, and cartilage, inducing inflammation and cartilage destruction during RA development [91], [92]. IL10, CCR5, and CCR4 mRNA levels were increased in RA patients' duodenal tissue, indicating immune cell activation. Only around 15% of individuals with established RA exhibited visible pathological changes in their intestinal tissue, such as partial or entire loss of superficial epithelium, an increase in plasma cells and granulocytes, and the formation of vasculitis lesions [95].

In RA, altered intestinal barrier permeability was also prevalent. Increased zonulin production, crucial for the integrity of tight junctions in the mucosa, has been linked to RA. Zonulin impairs intestinal barrier function by causing the disassembly of the tight junction complex proteins ZO1 and occludin. Gluten and dysbiosis can increase zonulin levels, altering intestinal barrier function. Gliadin, a gluten component, binds to the chemokine receptor

CXCR3 and destroys the small intestine, increasing intestinal permeability. An increase in zonulin levels has been linked to the beginning of new RA [95].

Bronchiectasis is a long-term disorder in which the lungs' airways enlarge, accumulating extra mucus that can render the lungs more susceptible to infection. ACPAs and RF have been found in individuals with bronchiectasis, implying a link between RA and bronchiectasis [95]. Tobacco use may potentially contribute to the development and activation of PAD [92].

According to an altered population of gut microbiota, a low abundance of *Bacteroides fragilis* and *Bifidobacterium* were found in Rheumatic patients, whereas the increased abundance of *Prevotella copri* and *Lactobacillus* were detected [90]–[93], [95]–[99]. High abundance of *Gordonibacter pamelaeae, Clostridium asparagiforme, Eggerthella lenta,* and *Lachnospiraceae bacterium*, whereas there is a low abundance of *Lactobacillus* spp., *Bifidobacterium dentium,* and *Ruminococcus lactaris* in the gut of RA patients [91], [92], [95]. Furthermore, there is a higher abundance of *Enterobacteriaceae* and *Klebsiella,* whereas there is a low abundance of *Bifidobacterium* in RA patients with a high level of TNF- α or IL-17A [97]. Increased abundance of *Bacteroides,* and *Escherichia-Shigella,* whereas a low abundance of *Lactobacillus, Alloprevotella, Enterobacter,* and *Odoribacter* were observed in a study for RA [97], [98]. The abundance of *Prevotella copri* was honoured to be associated with the absence of human leukocyte antigen (HLA)-DRB1 and the over-representation of these bacteria in new-onset untreated RA patients. In contrast, the abundance of *Prevotella copri* has been reported to decrease in treated RA patients [90], [91], [95]. Furthermore, *P. copri* can express the phosphoadenosine phosphosulfate reductase, which stimulates the production of thioredoxin. Thioredoxin has a crucial role in the pathogenesis of RA [91]. Another study detected a high abundance of *Lactobacillus salivarius* in active cases of RA. High serum of immunoglobulin, autoantibodies, anticyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF) were observed to be related to the presence of dysbiosis [91], [93]–[95], [99]. Furthermore, a low abundance of *Haemophilus* spp. was found in the fecal and oral culture of RA patients [94], [97], [99]. Also, a high level of α-aminoadipic acid and asparagine and the production of IL-17 was reported to be related to the presence of *Collinsella* in RA [97]. A high abundance of gram-positive *Cryptobacterium curtum* was detected in RA patients. These bacteria can alter the arginine pathway and modulate ACPAs [93].

Periodontal disease has been linked to RA. *Porphyromonas gingivalis* can cause protein citrullination, which increases ACPA production. *P. gingivalis* has been associated with elevated levels of anti-CCP antibodies in RA patients. *P. gingivalis* aggravates arthritis by changing the gut microbiota and increasing Th17 cells in the mesenteric lymph nodes.

Furthermore, pre-symptomatic people and RA patients had significant levels of anti-*P. gingivalis* virulence factor arginine gingipain B antibody. RA medicines were helpful in both RA and periodontitis, and they could lower the abundance of *P. gingivalis* as well as blood levels of RF and ACPA. Salivary IL-17 and IL-33 levels were shown to be elevated in RA patients independent of periodontal condition. A. As a result, this study casts doubt on the link between RA and periodontal disorders [93], [95], [96], [99]. *P. gingivalis* generates peptidyl-arginine deiminase (PAD), a citrullinating enzyme capable of citrullating both host and bacterial proteins. Anti-citrullinated peptide antibodies generated by the PPAD enzyme were discovered in higher amounts in individuals with pre-RA and RA. Citrullination is associated with a localized oral mucosal immune response in periodontitis, which has been linked to a systemic serum ACPA response, followed by synovial inflammation and RA[93], [94]. Lipopolysaccharide from *Porphyromonas gingivalis* has been demonstrated to suppress neutrophil apoptosis and promote epithelial production of IL-8, encouraging neutrophil migration towards periodontal tissue and into gingival crevices [93].

Other oral bacteria discovered in RA include *Aggregatibacter actinomycetemcomitans.* These bacteria boost citrullinated autoantigens and create leukotoxin-A (Ltx A), both of which have been seen in RA patients [93], [96]. In a study of *A. actinomycetemcomitans*, the bacterial toxin LtxA was demonstrated to promote membrane lysis, perhaps contributing to the hypercitrullination situation seen during NETosis [93].

Routine dental activities like teeth brushing, flushing, and chewing have been shown to direct enter oral microorganisms into the bloodstream. Another method for bacterial translocation hypothesized is the employment of host cells as a “Trojan horse”. *Prophyromonas gingivalis* is known to live intracellularly inside various cell types, including macrophages and dendritic cells, which may enter the bloodstream and spread germs throughout the body. Microbial translocation is of importance in the setting of RA because the presence of oral bacteria or their components in the synovial joints may trigger immune activation pathways and local inflammation [93].

Some antibiotics, such as clarithromycin, considerably influence RA symptoms [91]. Minocycline treats RA and can eliminate various bacteria, including *Actinobacteria*, especially *Collinsella* spp., and certain *Firmicutes* [95]. Methotrexate has been related to a decrease in the quantity of *Enterobacteriales* because it inhibits dihydrofolate reductase, which is also generated by the bacterium for growth [95], [100]. During sulfasalazine medication, there was a persistent reduction in *Clostridium perfringens, E. coli,* and *Bacteroides* spp. Hydroxychloroquine was found to increase the number of butyrate-producing bacteria

Faecalibacterium spp. In the feces of individuals on etanercept, a TNF blocker, there was an increase in the number of *Cyanobacteria* and *Nostocophycideae* and a decrease in the quantity of *Deltaproteobacteria* and *Clostridiaceae* [95], [97], [100].

Lactobacilli consider an important probiotic. A vegan diet, which is rich in *Lactobacilli,* improves the disease. *Lactobacillus rhamnosus* GR-1 and *L. reuteri* capsules showed a positive effect on RA. *L. casei* 01 supplementation and *Lactobacillus helveticus* HY7801 decrease the inflammatory immune response of RA. A study showed that *Bacillus coagulans* GBI-30, 6086 enhanced the patient pain assessment score for RA patients. Another study reported the efficacy of a mixture of *Lactobacillus acidophilus, Lactobacillus casei,* and *Bifidobacterium bifidum* over the administration of cellulose only, as the administration of probiotic combination improved the disease activity score of 28 joints [98], [100].

7. Altered Gut- Brain axis in chronic diseases

7.1. Cardiovascular diseases

Cardiovascular diseases (CVD) are disorders of the heart and blood vessels. It is frequently linked to the formation of fatty deposits in the arteries (atherosclerosis) and increases the risk of blood clots. It's also linked to artery damage in organs like the brain, heart, kidneys, and eyes. Despite significant progress in the treatment of CVD, some issues remain to be explained and investigated.

The gut-brain axis has been shown to play an important role in the pathogenesis of numerous cardiovascular diseases. The nervous system, in conjunction with the endocrine and sympathetic nervous systems, modulates the function of the cardiovascular system. On the other hand, altered gut microbiota and their metabolites SCFAs have a significant impact on CV system functions [5], [101].

Alterations in gut microbiota have been observed in coronary artery disease. In atherosclerotic CVD, there is a greater abundance of *Enterobacteriaceae* and *Streptococcus* spp. than in healthy participants. Furthermore, an increase in the abundance of the genus *Collinsella* has been reported, whereas the abundance of *Eubacterium* and *Roseburia* varies with age and gender. It is currently unknown how the microbiota influences the development of atherosclerosis. Trimethylamine N-oxide (TMAO) has been found to play an important role in CVD [5]. A high abundance of *Proteobacteria* was observed in a study carried out on 26

patients who had undergone the carotid endarterectomy. *Actinobacteria, Bacteroidetes* and *Firmicutes* were found in aortic plaque [102]. A study showed a high abundance of *Escherichia/Shigella* and *Enterococcus*, while a low abundance of *Faecalibacterium, Subdoligranulum, Roseburia*, and *Eubacterium*. *Faecalibacterium* has anti-inflammatory effect [103].

Atherosclerosis is the primary cause of CVD, particularly coronary artery disease, and can result in myocardial infarction. Increased lipids and fibrous tissue in the internal lining of arterial walls characterize atherosclerosis. The thickening of the inner wall of an artery reduces blood flow, resulting in a low supply of oxygen to the myocardial cell. Because of the lipid accumulation on the endothelial, monocytes bind to this forming layer and differentiate into macrophages, resulting in foam cells. Oxidation changes LDL particles into a dangerous chemoattractant. A cascade of cytokines and growth regulatory peptides regulates cell adhesion, differentiation, and proliferation, and interaction with the matrix results in the formation of fatty streaks as a result of an interaction with the matrix [103]–[105]. TMAO promotes the formation of atherosclerosis by increasing the formation of foam cells and the progression of atherosclerotic plaques. It also activates the inflammatory pathway, causing leukocytes to become activated. It promotes platelet hyperresponsiveness and thrombosis formation [103], [105], [106]. Some bacteria in atherosclerotic plaque have been observed, such as *Streptococcus, Pseudomonas, Klebsiella, Veilonella* spp., *Chryseomanas* and *Chlamydia pneumoniae* [105], [107].

Hypertension is the most common CVD in the world, and it is the leading cause of numerous complications that reduce quality of life or increase morbidity and mortality. It has been reported that some dysbiosis, such as *Klebsiella* spp., *Streptococcus* spp., *Parabacteroides merdae, Desulfovibro,* and *Prevotella*, play a role in the pathogenesis and severity of hypertension [5], [105]. Furthermore, hypertensive patients were found to have lower SCFA production and a shift in the *Firmicutes* to *Bacteroidetes* ratio. After minocycline administration, the efficacy of microbiota as a potent antihypertensive was reported in patients with resistant hypertension [101]. A low abundance of SCFAs-producing bacteria was reported, such as *Ruminococcaceae, Roseburia,* and *Faecalibacterium* [105].

The importance of SCFAs in modulating the endocrine system, nervous system, inflammation, and gut homeostasis is well known. SCFAs bind to G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), G protein-coupled receptor 109A (GPR109A), and vascular olfactory receptor 78 (VOR78) (Olfr78). Because it is expressed in olfactory neurons, renal afferent arterioles, and vascular smooth muscle cells, Olfr78 plays a

role in blood pressure regulation. Olfr78 has been shown to raise renin levels, which raise blood pressure via the Aldosterone-renin-angiotensin axis. GPR41, on the other hand, can counteract this effect. Following the response to propionate, the roles of Olfr78 and GPR41 were observed. SCFAs have also been shown to have a vasorelaxant effect, while other studies explain the impact of vasodilation due to GPR41 as it decreases the level of cAMP through Gαi [5], [107]–[109]. There is a link between hypertension and butyrate-producing bacteria, as a low abundance of the genus *Odoribacter* was related to higher systolic pressure in obese pregnant women [104]. Dietary salt intake elevates the blood pressure, as well as changes the composition of Gut bacteria, as high salt intake is associated with a high abundance of *Lachnospiraceae, Ruminococcus,* and *Parasutterella* spp., and a low quantity of *Lactobacillus* and *Oscillibacter* [105], [107]. Butyrate, one of the SCFAs, has been observed to lower blood pressure [105].

Heart failure, also known as congestive heart failure, occurs when the heart muscle fails to adequately pump blood. When this happens, blood often backs up, and fluid can build up in the lungs, causing shortness of breath. Certain heart conditions, such as coronary artery disease or high blood pressure, gradually weaken or stiffen the heart, rendering it incapable of properly filling and pumping blood. There was an increase in the abundance of *Candida*, *Campylobacter*, *Yersinia*, and *Shigella* in fecal cultures of patients with chronic heart failure compared to controls. It is hypothesized that the altered environment of gut bacteria, as well as changes in intestinal barrier permeability caused by low cardiac output and decreased blood supply to the intestine, result in an increase in circulating endotoxin, which accelerates systemic inflammation. TMAO is also involved in the pathogenesis of heart failure. Furthermore, p-cresyl sulfate (PCS) and phenylacetylglutamine (PAG) are important in disease development [5], [101], [102], [106], [107], [109].

Lipopolysaccharide (LPS), also known as endotoxin, is transported from the gut lumen to the circulatory blood system because of gut barrier dysfunction and increased intestinal permeability. Gram-negative bacteria produce LPS-containing outer membrane vesicles (OMVs). LPS binds to TLR4 and activates NF-kB signaling, resulting in an overproduction of proinflammatory cytokines and adhesion molecules, leading to atherosclerosis. In addition to the LPS/TLR4/NF-kB signaling pathway, LPS can be internalized to the cytosol via endocytosis and released into the cytosol, where it activates caspase-11, resulting in further activation of the NLRP3 inflammasome, in turn; increase in the secretion of IL-18 and IL-1 β [102], [104], [105], [110]. Administration of canakinumab, which is an inhibitor of IL-1 β, was

reported to be efficient in lowering the level of lipid, so it is proposed to be used in the treatment of CVD [105], [106], [108].

Primary bile acids (BAs) are secreted into the duodenum and aid digestion and absorption by emulsifying lipid-soluble dietary substances and vitamins. BAs also have strong microbial activity, and they take part in signaling molecules, acting as ligands for nuclear receptors and thus influencing metabolism. For example, activation of the farnesoid-X-receptor (FXR) inhibits the action of the cholesterol 7 α-hydroxylase enzyme, which is required for the formation of primary BAs from its cholesterol precursor. The gut microbiota modifies primary BAs in the intestine via bacterial salt hydrolase activity, which removes the OH groups, converting them to secondary BAs. Because primary BAs are toxic to bacteria, they are rendered insoluble, providing the bacteria with a mechanism to reduce toxicity. BAs may be further modified by the gut microbiota before being returned to the liver for re-conjugation and reintroduction into circulation. BAs are an essential pathway for cholesterol elimination via feces, lowering circulating cholesterol levels and the risk of plaque buildup. The gut microbiome can reduce the rate of BA formation, raising LDL levels in the blood and increasing the risk of atherosclerosis [103], [106]–[111].

Trimethylamine N-oxide (TMAO) has a vital role in the development of CVD. TMAO, a bacterial metabolite, is produced because of the metabolism of phosphatidylcholine, choline, carnitine, γ-buytrobetaine, betaine, trimethyl lysine, valerobetaine and ergothioneine. The biosynthesis of TMAO is divided into two steps: A) firstly, the cleavage of precursors with structural moiety containing trimethylamine (TMA) group to form TMA, which is catalyzed by bacterial enzymes, such as choline TMA lyase (CutC/D), carnitine Rieske-type oxygenase/reductase (CntAB), YeaW/X, betaine reductase, and ergothionase. B) the second step is the oxidation of TMA to TMAO by hepatic flavin monooxygenase (FMO) [102]–[113]. Through multiple mechanisms, TMAO is linked to atherosclerotic CVD and thrombosis. First, TMAO increases endogenous macrophage expression of scavenger receptors, CD36 and SR-A1, resulting in the uptake of modified LDL and the formation of foam cells. Second, TMAO inhibits the expression of two key bile acid synthetic enzymes, Cyp7a1 and Cyp27a1, as well as multiple bile acid transporters (Oatp1, Oatp4, Mrp2, and Ntcp) in the liver, resulting in a reduction in bile acid pool size and subsequent cholesterol excretion. Third, TMAO promotes the recruitment of activated leukocytes to endothelial cells by activating MAPK, NF-B, and ROS-TXNIP-NLRP3 inflammasome signaling. TMAO also causes intracellular Ca2+ release and platelet aggregation, resulting in thrombosis [102], [113]. TMA-containing nutrient L-

carnitine is a precursor used by gut bacteria to form TMA and TMAO. Red meat, liver, and egg yolk are high in L-carnitine and choline. This explains the increased risk of CVD due to red meat consumption [104], [107], [112], [113]. TMAO was found to change the size and composition of bile acids [112]. TMAO was observed to enhance the platelet aggregations, even so in the presence of low-dose Aspirin. Low-dose aspirin prevents platelet aggregation and prophylaxes against atherosclerotic plaque formation. That means, the involvement of TMAO in aspirin resistance [107], [108], [113].

Indoxyl sulfate is a tryptophan metabolite derived from the gut microbiome. The metaorganismal biosynthesis of indoxyl sulfate includes microbial cleavage of tryptophan to indole, which is then oxidized to indoxyl and finally conjugated as indoxyl sulfate in the liver. Tryptophanase, a microbial enzyme that converts tryptophan to indole, has been discovered in *Lactobacillus*, *Bifidobacterium longum*, *Bacteroides fragilis*, *Parabacteroides distasonis*, *Clostridium bartlettii*, and *E. hallii*. Indoxyl sulfate influences the pathogenesis of CVD through different mechanisms. By oxidative stress, it can cause endothelial dysfunction, including inhibition of proliferation and nitric oxide production, like in human umbilical vein endothelial cells (HUVEC). Indoxyl sulfate can also stimulate monocytes to release TNF via the aryl hydrocarbon receptor (AhR), which then stimulates human vascular endothelial cells to produce CX3CL1, which recruits CD4(+) CD28(-) T cells, which have the cytotoxic capability and induces apoptosis in HUVECs, resulting in vascular endothelial cell damage. Indoxyl sulfate is also thought to be a pro-thrombotic agent. It stimulates platelet activity by increasing platelet-derived microparticles and platelet-monocyte aggregates, as well as causing an increased response to collagen and thrombin. Furthermore, indoxyl sulfate impairs oxygen sensing in EPO-producing cells, suppressing EPO production and resulting in anemia [102], [110].

P-cresyl sulfate (PCS) is a tyrosine metabolite which is produced by the gut microbiota that is processed in four steps: the first to the third steps are carried out in gut microbes to form intermediates, 4-hydroxyphenylpyruvate, 4-hydroxyphenylacetate, and p-cresol. The final step is to form PCS in gut mucosa or liver. PCS, like indoxyl sulfate, induces NADPH oxidase activity and reactive oxygen species production, which contributes to direct cytotoxicity to cardiomyocytes, facilitating cardiac apoptosis and resulting in diastolic dysfunction [102], [110].

Phenylacetylglutamine (PAG) is a metabolite of phenylalanine, which is produced by gut microbiota. It can replace the urea in patients with lacked carbamyl phosphate synthetase. Accumulation of PAG leads to uremia. In the human liver and kidney, aminotransferase, and

pyruvate, especially ferredoxin oxidoreductase A (PorA), were involved in the conversion of phenylalanine to phenylacetic acid, as well as the activation of phenylacetic acid to form phenylacetyl-CoA and ligate to glutamine. Aminotransferase and PorA were reported to be produced by *Clostridium sporogenes* [102], [108].

Several uremic toxins, including advanced glycation end products (AGEs), phenols, and indoles, can be produced by gut microbiota. Toxins enter the bloodstream and are filtered by the kidneys. While impaired kidney function leads to the accumulation of these toxins, inducing an inflammatory response and thus hastening the progression of chronic kidney disease. A link between high levels of uremic toxin and cardiovascular risk has been proposed. In patients with chronic kidney disease, an elevated level of indoxyl sulfate was linked to aortic classification, increased vascular stiffness, and an increased risk of cardiovascular mortality. After treatment with the oral adsorbent AST-120, there was an increase in flow-mediated, endothelium-dependent vasodilation in association with a low level of indoxyl sulfate [101]. In elderly hemodialysis patients, PCS predicts cardiovascular events and all-cause mortality. Elevated serum PAG levels are associated with overall mortality and CVD in patients with chronic kidney disease [102].

Gut microbiotas produce some beneficial metabolites. Esculin is one of these beneficial metabolites. Gut microbes can hydrolyze it to release free esculetin, which inhibits hydrogen peroxide and Ang-II-induced cell death in human aortic endothelial cells. This is carried out by increasing NO production through AMPK-mediated eNOS phosphorylation. Anthocyanin, a polyphenol compound, has the potential to act as an antiplatelet agent, thereby preventing thrombosis and CVD. Early, a study found that protocatechuic acid, a gut microbiota metabolite of anthocyanin, decreases miR-10b expression in macrophages, increasing ABCA1 and ABCG1 expression and enhancing cholesterol reverse transport, resulting in atherosclerosis reduction. In addition, it has antioxidant properties. Another natural polyphenol, ellagitannin, found in some fruits, nuts, tea, and seeds like pomegranates, berries, and walnuts, has been observed to affect positively on the cardio system. Because of its very low bioavailability, most ellagitannin intake does not reach the circulatory system, but gut microbes can metabolize ellagitannin into urolithin A or B, which can be absorbed into the circulatory system. *Gordonibacter urolithinfaciens* sp. nov. and *Bifidobacterium pseudocatenulatum* INIA P815 are known as urolithin-producing gut bacteria. Urolithin A can inhibit endothelial cell migration and decrease the expression of chemokine (C-C motif) ligand 2 and interleukin-8, thereby alleviating TNF-induced inflammation and associated molecular markers in human aortic endothelial cells, whereas urolithin B-glucuronide can activate eNOS

expression, thereby alleviating TNF-induced inflammation and associated molecular marker, which may be beneficial to prevent CVD. Enterolactone, another bacterial metabolite polyphenol compound, has antioxidation effect [102], [110].

The gut microbiota also influences the efficacy of CVD drugs. Statins are the most used drugs in CVD because they lower lipid levels, particularly LDL cholesterol. In one study, it was discovered that patients with statin-sensitive responses had higher levels of *Lactobacillus, Eubacterium, Faecalibacterium*, and *Bifidobacterium*, while patients with resistance responses had lower levels of *Clostridium.* It has been proposed that statin sensitivity is linked to increased bile salt hydrolase, which plays a role in cholesterol metabolism. Monacolin k, another natural statin, loses bioactivity due to gut microbiota catabolization of its acid form. Digoxin, a drug used to treat heart arrhythmias, is metabolized by *Eggerthella lenta* into dihydrodigoxin, which inhibits the drug's action. Aspirin, on the other hand, demonstrated a discrimination effect on gut bacteria in four taxa: *Prevotella* spp., *Bacteroides* spp., *Ruminococcaceae* family, and *Barnesiella* spp [102], [106].

Probiotics like *Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus,* and *Enterococcus* may be used to treat CVD. Prebiotics can help with treatment because they promote the growth of beneficial bacteria. Most probiotics are carbohydrates found in fruits, vegetables, and cereals [5], [103]. B-Glucan is a prebiotic that can help lower cholesterol and maintain blood glucose homeostasis. It has been reported that glucan improves endothelial function, which has a cardioprotective effect [103].

In the treatment of CVD, inhibiting the effect of TMAO is a logical target. Modifying one's diet is one possible intervention to slow the progression of CVD. Limit your intake of TMAO-containing foods such as red meat, fish, high-fat dairy products, and some nuts. Another possibility is to regulate the microbial metabolism of TMAO by modifying the genes responsible for expressing the metabolic enzymes. Inhibiting hepatic FMOs, which contribute to TMAO production, is the third option. TMAO can be produced by FMO1, FMO2, and FMO3[112], [113]. Resveratrol is a passionate dietary intervention in the treatment of CVD, as it attenuates TMAO by inhibiting TMA generation. Resveratrol is found in grapes and berries [5], [102], [113]. 3, 3-dimethyl1butanol, is a passionate medication, a non-lethal inhibitor of TMA formation, reduces atherosclerotic lesions by decreasing the levels of TMAO converted from TMA. According to one study, methimazole and indole binding could provide evidence for the development of human FMO3 inhibitors. The inhibitory activity of human FMO3 was attributed to Indole-3-carbinol (I3C) and its acid condensation products, I33' and LT [5], [103], [107], [110], [113]. *Methanomassiliicoccus luminyensis B10* can lower TMA by

metabolizing TMA into methane [109]. Meldonium is an aza-analogue of γ-butyrobetaine (GBB), as it is a competitive inhibitor to GBB and L-carnitine, so it is used commercially to reduce the level of L-carnitine. However, meldonium hasn´t any effect on gut bacteria [113].

Unsaturated fatty acids, particularly n-3 polyunsaturated fatty acids, are widely regarded as cardioprotective. Animal oil is primarily obtained from fish, whereas flaxseed oil is obtained from plants. Both fish oil and flaxseed oil have been shown to modulate gut microbiota and increase microbial production of SCFAs, promoting the growth of SCFA-producing bacteria and decreasing microbial production of LPS. Both oils have been linked to a reduction in TMAO, considering the fish oil is the most effective in exacerbating atherogenesis. Beta-glucan is a natural polysaccharide found in plant cell walls that are considered a prebiotic because it promotes the growth of beneficial intestinal bacteria, produces SCFA and lowers blood cholesterol and glucose levels, all of which lowers the risk of CVD [104], [107], [111].

Quercetin belongs to the flavonoid family, which is a subclass of polyphenols and is thought to have antioxidant and anti-inflammatory properties. It significantly altered the composition of several bacterial species, increasing the abundances of *Bacteroides vulgatus* and *Akkermansia muciniphila,* which have been linked to obesity, while it decreases the abundances of *Eubacterium cylindroides* and *Bilophilia wadsworthia.* Quercetin and its metabolites have been shown to increase the expression of adenosine monophosphate-activated protein kinase (AMPK). The enzyme AMPK is involved in cellular energy homeostasis and fatty acid oxidation. The positive effects were reduced when AMPK was inhibited. Quercetin and its metabolites activated AMPK and endothelial nitric oxide synthase in human aortic endothelial cells, resulting in an increase in nitric oxide, a potent vasodilator [103].

Phytoestrogens bind to estrogen receptors, either mimicking estrogen or acting as an antagonist. Thus, phytoestrogens' effects can be biphasic: for example, phytoestrogens increase vasodilation and nitric oxide metabolism, which may be beneficial to vascular health; however, phytoestrogens may also have some prothrombotic or pro-inflammatory effects. Enterolactone is a biphenol that acts as an antioxidant. In a study, a high level of enterolactone was associated with lower CVD mortality. Furthermore, urinary total and individual phytoestrogens were found to be significantly inversely related to serum CRP. Enterolactone and Enterodiol can reduce the effect of lipopolysaccharide on peripheral blood lymphocytes [110].

7.2. Stroke

Stroke is a life-threatening condition that is a leading cause of death. It is distinguished by a central nervous system neurological deficit caused by either cerebral infarction or intracerebral hemorrhages [114]. There are two types of strokes: ischemic stroke and hemorrhagic stroke. Ischemic stroke occurs because of a blockage of cerebral blood flow. Excitotoxicity, oxidative stress, neuroinflammation, apoptosis, amyloid production, and tau dysfunction all contribute to the resulting brain damage. Dementia is accompanied by post-ischemic brain due to amyloid plaque and neurofibrillary tangle accumulation [115].

To understand the role of the gut-brain axis in stroke, we can follow these possible mechanisms. Mucosa has a unique anatomic structure that is part of the autonomic nervous system. Following a stroke, increased noradrenaline release and decreased acetylcholine result in changes in cecal mucoprotein production. Increased intestinal permeability is thought to be due to the activation of corticotropin-releasing and glucocorticoid hormones, as well as bacterial localization rearrangement. This alteration caused by dysbiosis may lead to hypertension and its vascular consequences. The immune system is the next possible mechanism. Activated T-cells migrate to the brain within 2-3 days of a stroke, which was observed in animal models. They localized in the leptomeninges and secreted IL-17 (IL-17+ γδ T cells), resulting in increased chemokine production and cytotoxic cell infiltration of the brain (neutrophils and monocytes). Treg cells secrete the anti-inflammatory cytokine IL-10, which plays a protective role in ischemic brain injury. Treg cells were found at a higher level in the small intestine, but they did not enter the brain parenchyma after stroke. In contrast, Treg cells were found post-stroke to inhibit IL-17+ T cell proliferation. Increased IL-17 levels are a significant risk factor for embolic stroke because they make atherosclerotic plaques more vulnerable. Furthermore, pro-inflammatory activity is linked with a high abundance of *Lactobacillus ruminis* subgroup and increased production of IL-8. As a response to damaged brain tissue, microglia and astrocytes are released to contribute to an inflammatory response, accompanied by a release of anti-inflammatory mediators. The level of some organic acid is related to the severity of a stroke. It worsens when butyrate levels are low and glycosylated hemoglobin and LDL cholesterol levels are high. Stroke patients had elevated levels of valeric acid and CRP [8], [116].

Gastrointestinal complications following a stroke cause a delay in the medical response to treatment. Many studies have shown that gut bacteria can be a risk factor for stroke and influence the prognosis after a stroke [115], [116].

A low abundance of *Bacteroidetes* has been detected in a fecal culture of patients with ischemic stroke after two days after admission. A study has found that in post-stroke patients, there was a low abundance of *Streptococcus,* either the good bacteria such as *Streptococcus thermophilus* or the harmful bacteria *Streptococcus pneumonia. Enterobacter, Megasphaera,* and *Oscillibacter* have been observed in ischemic stroke patients with a low abundance of *Bacteroides, Prevotella,* and *Faecalibacterium*. In addition, a high abundance of *Atopobium* and *Lactobacillus ruminis* and a low abundance of *Lactobacillus sakei* were detected in stroke patients. Another study has detected a high abundance of *Escherichia, Parabacteroides,* and *Ruminococcus* in stroke patients. Also, a significantly elevated abundance of *Odoribacter, Akkermansia, Ruminococcaceae, Flavobacteriaceae,* and *Victivallis* have been noticed in stroke patients. Another observation was the low level of butyrate-producing bacteria found in patients with a high risk of stroke. A high level of LP has been found to be the reason for brain neuroinflammation, BBB alteration, brain edema, and complication after stroke [8], [115]–[117].

As previously stated, LP plays a role in the stimulation of systematic inflammation by altering the intestinal mucosa barrier and inducing pro-inflammatory cytokines such as INF-γ, IL-6, and TNF- α. It is proposed that after a cerebral infraction, gut dysbiosis and chronic systemic inflammation play a role. Dysbiosis has been shown to inhibit the transport of effector T cells from the intestine to the leptomeninges [115].

Amyloid peptides are associated with being the stone for the formation of brain amyloid, which can be produced by *Enterobacter* spp. Microbial amyloid enhances the amyloid aggregation, triggering the inflammation response. It is still now not clear how microbial amyloid change tau protein or builds β- amyloid peptides. Microbial amyloid affects brain gliosis; thus, it can control brain inflammation and β- amyloid levels. That is why it is suggested that microbial amyloid has a role in the activation of microglia to phagocytose amyloid and tau protein [8], [115].

TMAO is also related to stroke. A low level of folic acid besides a high level of TMAO has been observed in stroke patients. Its role in platelet aggregation is mediated by an augmented release of ca2+ from intracellular stores. As previously explained, the pathway of TMAO production and its availability in many foods, mainly in the red meet. TMAO has effect on cholesterol metabolism and endothelial dysfunction [8], [115], [118].

Although antibiotics have an anti-inflammatory effect, their use as a preventative measure in stroke is inconclusive. The use of ceftriaxone in adult patients with ischemic or hemorrhagic patients reduced infection rates but did not improve outcome, shorten hospitalization time, or reduce mortality. These findings came from the Preventive Antibiotic in Stroke Study (PASS). Other probiotics or prebiotics that are used are like those used in CVD. Lowering TMAO levels, whether through resveratrol, 3-3-d imethyl-1-butanol, or reducing consumption of TMA-rich foods, is an important goal [8], [116], [118].

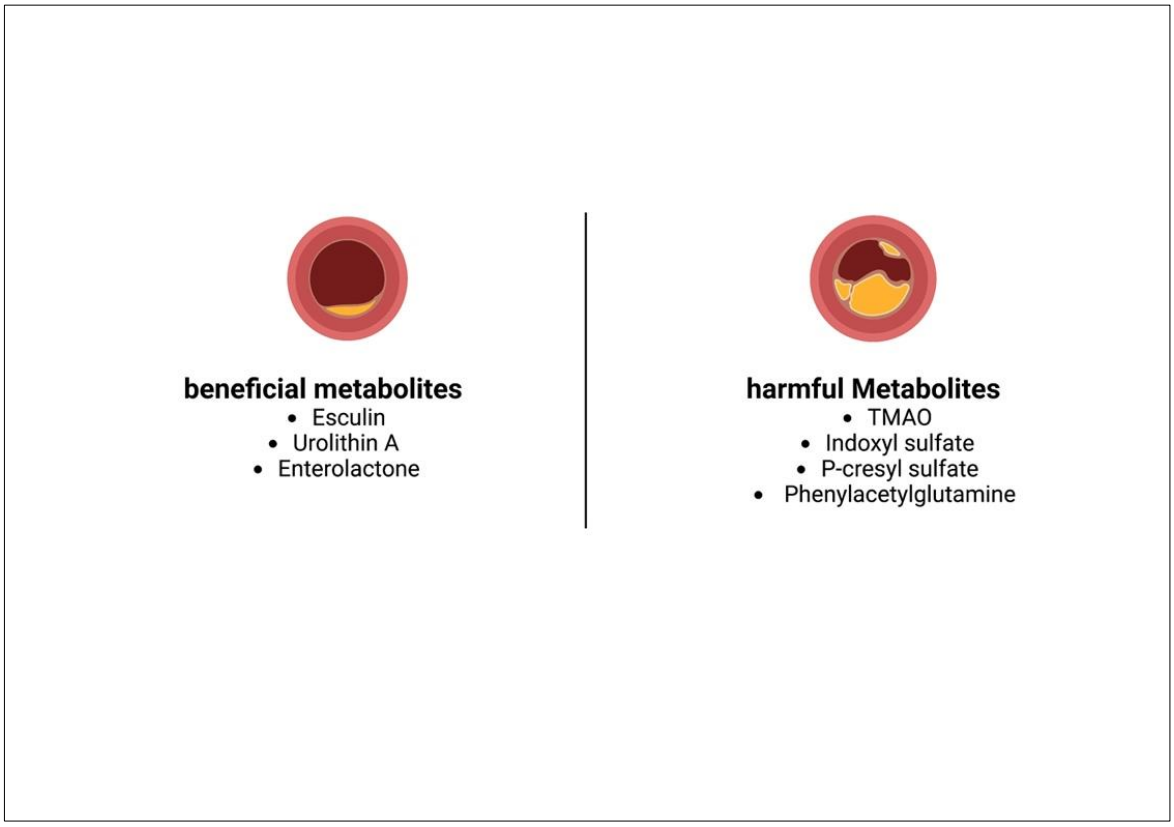

Figure 3. Beneficial and toxic compounds, generated in blood vessels by gut bacteria that play a crucial impact in cardiovascular disease are depicted schematically [102], [110].

7.3. Diabetes

Diabetes is a chronic metabolic condition characterized by high blood glucose levels that, over time, causes significant damage to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes is classified into several categories, the most well-known of which are type 1 diabetes (T1D) and type 2 diabetes (T2D). The most prevalent kind of diabetes, which mainly affects

adults, happens when the body develops insulin resistance or fails to generate enough insulin. Diabetes type 1 is a chronic disease in which the pancreas secretes little or no insulin. The gut microbiota influences the immune response, intestinal barrier permeability, glucose and lipid metabolism, and insulin sensitivity, making the Gut-Brain axis critical in diabetes.

7.3.1. Type 2 Diabetes

An altered bacteria environment in the gut of patients with T2D has been observed. Low abundance of *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia* and *Roseburian* were associated with T2D, whereas the high quantity of *Rumminococcus, Fusobacterium,* and *Blautia* were reported [6], [119]. Other studies have observed a low abundance of butyrate-producing bacteria, such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii*. In contrast, a high quantity of *Bacteroides caccae, Eggerthella spp., Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum,* and *E. coli* has been found in T2D. In addition, a low abundance of *Akkermansia muciniphila* was found in newly diagnosed patients with T2D, thus is suggested to use these bacteria as a biomarker for glucose intolerance [6], [120]–[127]. Another Study detected the presence of *Acidaminococcus, Anaerostipes, Aggregatibacter, Blautia, Dorea, Desulfovibrio,* and *Faecelibacterium* in the gut of diabetic patients [122]. The abundance of *Blautia, Odoribacter, Oscillibacter,* and *Pseudoflavonifractor* was positively related to insulin resistance; from that, *Blautia* was associated with impaired glucose tolerance in T2D [124]. In another study, a higher abundance of *Lactobacillus* spp. was observed in diabetic patients than in non-diabetics, positively associated with fasting glucose and glycated hemoglobin (HbA_{1c}) levels. In contrast, *Clostridium* spp. was negatively linked to fasting glucose, $HbA_{1c,}$ insulin, C-peptide, and plasma triglyceride. However, *Clostridium* spp. was positively correlated to high-density lipoprotein (HDL) cholesterol [125].

A high-fat diet (HFD) can boost pro-inflammatory cytokines, gut flora, and their products, which is frequent in T2D patients. An increase in LPS levels promotes metabolic endotoxemia and low-grade inflammation. TLRs, the NLRP3 inflammasome, and NOD-like receptors (NLRs) expressed on the surface of macrophages and dendritic cells bind to LPS. LPS also stimulates the TLR4/MyD88/NF-kB pathway in blood and tissues, producing pro-inflammatory chemicals such as TNF-α, IL-1, IL-6, and iNOS. Activated serine kinases (JNK and IKK) can promote IRS (insulin receptor substrate) serine phosphorylation, which inhibits insulin signaling and results in cellular insulin resistance (IR) [6], [119]–[124], [127].

Ruminococcus gnavus and *Fusobacterium nucleatum* promote several inflammatory cytokines. In contrast, the role of other bacteria is beneficial, such as *Roseburia intestinalis* induces IL-10, increases IL-22 production, restores insulin sensitivity, lowers the production of INF-γ, and suppresses the activity of IL-17. *Roseburia intestinalis* can induce the proliferation of T regulatory cell, TGF- β and inhibit intestinal inflammation. Other beneficial bacteria suppress inflammation, such as *L. plantarum, L. paracasei, and L. casei,* as they decrease IL-1 β, monocyte chemoattractant protein-1, Intercellular adhesion molecule-1, IL-8, CD36 and CRP. *Akkermansia muciniphila, Bacteroides fragilis, Lactobacillus plantarum* and *L. casei* are involved in glucose metabolism in muscles, protecting the muscles from insulin resistance and inhibiting TNF-α. *Roseburia* and *Faecalibacterium* produce the butyrate, which can inhibit NF-kB [119], [122], [124].

T2D increases intestinal permeability, allowing bacterial metabolites to enter the systemic circulation and cross the BBB to reach the brain. Stimulating AMP-activated protein kinase (AMPK) in the intestinal epithelium aids *Akkermansia muciniphila* in improving tight junctions via extracellular vesicles. *Akkermansia muciniphila* (*Amuc* 1100) outer membrane increases the production of occluding and tight junction protein-1 (Tjp-1) and enhances gut integrity. *Amuc* 1100 inhibits cannabinoid receptor type 1 (CB1) activation in the stomach, lowering gut permeability and LPS levels. Butyrate, which *Roseburia* and *Faecalibacterium generate,* can increase gut integrity via the serotonin transporter and PPAR- pathway, as well as mucin formation [6], [119], [123]–[127]. *Bacteroides* can modify intestinal mucus and glycocalyx, which influences intestinal permeability. Furthermore, *Bifidobacterium* spp. can preserve the epithelial barrier's tight connection [122].

Gut microbiotas impact glucose metabolism and insulin resistance in the liver, muscle, and fat tissue, which influences T2D development. They also impact the intestine's gut hormone synthesis, sugar absorption, and metabolism. *Bifidobacterium lactis* promotes glycogen production while decreasing the expression of gluconeogenesis-related genes in the liver. Furthermore, these bacteria can enhance glucose transporter-4 (GLUT-4) translocation and insulin-stimulated glucose absorption. *Lactobacillus gasseria* BNR17 increases GLUT-4 expression in muscle as well. *Akkermansia muciniphila* and *Lactobacillus plantarum* reduce the expression of hepatic flavin monooxygenase 3 (Fmo3). *Lactobacillus casei* can reduce insulin resistance by increasing mRNA levels of phosphatidylinositol-3-kinase (PI3K), insulin receptor substrate2 (IRS2), AMPK, Akt2 and glycogen synthesis in the liver. *L.rhamnosus* increases adiponectin levels in the epididymal fat, improving insulin sensitization. *Lactobacilli* and *Akkermansia muciniphila* have strong alpha-glucosidase inhibitory activity. This enzyme

prevents the breakdown of complex carbohydrates and reduces postprandial hyperglycemia. Microbiota and their products have been shown to improve insulin resistance and glucose tolerance by modulating gut hormones and enzymes. Butyrate can bind to G-protein coupled receptors (GPCR41 and GPCR43) in the gut, promoting the release of gut hormones: peptide 1 like glucagon (GLP-1), PYY, and GLP-2 from enteroendocrine cells. Thus, butyrate enhances insulin secretion and sensitivity [119]–[122]. SCFA can also act as signaling molecules, activating various pathways such as the AMP-activated protein kinase (AMPK) in liver and muscle tissues, activating key factors involved in cholesterol, lipid, and glucose metabolisms, such as peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1), peroxisome proliferator-activated receptor gamma (PPAR- γ), and Liver X receptors (LXR). Furthermore, SCFA has been demonstrated to activate Glucagon-like peptide-1 (GLP-1) via G-protein coupled receptor 43 (GPR43), also known as free fatty acid receptor 2 (FFAR2). FFAR2 is an SCFA receptor, that has been demonstrated to be activated by acetate, propionate, and butyrate. Another receptor for SCFAs is GPR41, also known as FFAR3, which is activated by propionate and butyrate. Both receptors FFAR2, FFAR3 can enhance the gut hormone peptide YY (PYY) and GLP-1 [6], [123]–[126], [128]. Due to the beneficial effect of GLP-2 on intestine integrity, the increase in expression of proglucagon, a GLP-2 precursor, with the help of gut microbiota improves the production of the enteroendocrine peptide and the number of epithelial enteroendocrine L-cells [126].

Bile salt hydrolases, which Lactobacillus produces, convert primary conjugated bile salts into deconjugated bile acids (BA). The deconjugated form converts then into secondary BA. Secondary BA induces GLP-1 production through G-protein-coupled bile acid receptor 1 (TGR5), modulating the expression of farnesoid X receptor (FXR) and fibroblast growth factor 15 (Fgf15), leading to the regulation of hepatic glucose metabolism and insulin sensitivity [6], [119], [120], [122], [128].

Obesity is a significant risk factor for metabolic syndrome and diabetes. Increasing fatty acid oxidation and reduction of fatty acid synthesis improve the pathogenesis of T2D. It has been shown that *Akkermansia muciniphila*, *Bacteroides acidifaciens*, *Lactobacillus gasseri*, and short-chain fatty acids promote fatty acid oxidation in adipose tissue. *Akkermansia muciniphila* has been shown to enhance the levels of 2-oleoylglycerol (2-OG), 2-palmitoylglycerol (2-PG), and 2-acylglycerol (2-AG) in adipose tissue, hence increasing fatty acid oxidation and adipocyte differentiation. Additionally, *Bacteroides acidifaciens* enhances fatty acid oxidation in adipose tissue via the TGR5-PPAR- α pathway. Butyrate can boost fatty acid oxidation and thermogenesis in the muscle by suppressing the histone deacetylation

process. This process raises energy expenditure by enhancing the muscles' mitochondrial activities. SCFAs reduce PPAR- γ expression in the liver and adipose tissue, which promotes fatty acid oxidation. *Lactobacillus gasseri* has been proven to lower obesity by boosting genes associated with fatty acid oxidation and reducing those related to fatty acid synthesis [6], [119].

The involvement of branched-chain amino acids (BBCA), which are generated by gut bacteria, has been linked to the development of T2D. Many studies have found a relationship between dietary consumption of BBCA and raised blood levels of BBCA, and an increased risk of T2D. A high abundance of *Prevotellacopri* and *Bacteroides vulgatus* is associated with a high level of BBCA in individuals with insulin resistance. Furthermore, obesity and pro-inflammatory circumstances are linked to decreased BBCA catabolism in peripheral tissue, particularly a decrease in adiponectin synthesis. BBCA is thought to affect insulin, glucagon, GLP-1, and glucose-dependent insulinotropic polypeptide (GIP) production [6], [120], [122], [124].

The gut microbiota uses tryptophan to make 3-indole propionic acid (IPA). It can translocate in a methodical circulation. IPA has antioxidant and anti-inflammatory characteristics and the ability to boost glucose metabolism and sustain β-cell functioning. Diabetes may be detected with plasma IPA [122].

TMAO is not only related to cardiovascular diseases but also diabetes. Gut bacteria produce TMA from dietary nutrients, such as choline and L-carnitine. TMAO is synthesized because of the metabolism of TMA by flavin monooxygenase 3 (FMO3) in the liver. A higher concentration of TMAO has been observed in T2D. In the POUNDS lost trial, improvement in insulin sensitivity was found when the level of TMAO, choline, and L-carnitine was decreased [120], [122], [124].

Hydrogen sulfide (H_2S) is produced from fermented proteins. H_2S can modulate the pathogenesis of diabetes because it modulates insulin sensitivity, adipose tissue lipolysis, inflammation and adipokine production. It induces hepatic gluconeogenesis and glycogenolysis and inhibits glucose utilization and glycogen stockpiles. The investigations supposed the role of pancreatic H_2S in the development of T2D. This hypothesis suggests the involvement of sulfate-reducing bacteria, such as *Desulfobacter, Desulfobulbus, Desulfovibro,* and *Desulfotomaculum*. H_2S can also be produced by anaerobic bacteria, such as *Salmonella enterica, Escherichia coli, Clostridia* and *Enterobacter* [122].

Oral bacteria can be transported to the gut, altering its microbiota and perhaps its immune system. Oral microbes have been shown to induce illnesses synergistically or cooperatively, and oral disorders (e.g., caries, periodontal disease) and T2D appear to be

mutually associated. Several studies have found substantial changes in the oral microbiome between T2D patients and non-diabetic people. Oral microbial indicators for T2D screening, diagnosis, and prognosis have been found. Diabetes can alter the bacterial environment of the mouth. Thus, oral bacteria's role in the pathogenesis of diabetes [6].

7.3.2. Type 1 Diabetes

T1D is primarily caused by a genetic defect and epigenetic and environmental factors. In recent years, a greater incidence rate of T1D has been found that is not explained by inherited factors and has been linked to changes in our lifestyle such as nutrition, cleanliness, and antibiotic usage, all of which might theoretically directly affect the microbiota. The Diabetes Prevention and Prediction (DIPP) study discovered a variation in the makeup of gut flora. Furthermore, a low amount of mucin, due to a lack of butyrate and lactate-producing bacteria, has been observed to causes β-cell autoimmunity and T1D [6], [128]. An acetate-rich diet is thought to reduce the number of autoimmune T cells in lymphoid tissues. On the other hand, the butyrate-rich diet increases the number and activity of regulatory T cells. LPS influences autoimmune regulation. LPS generated by *E. coli* helps to block innate immune responses, but LPS produced by *Bacteroides dorei* has little effect on T1D incidence [6], [123]. LPS also plays a vital role in increasing pro-inflammatory cytokines and compromising pancreatic β-cell function, which leads to diabetes. T1D is defended against by regulatory T (Treg) cells. A modest dosage of IL-2 increased the number of Treg cells in an animal investigation. The low concentration of *Clostridiales, Bacteroides, Lachnospiraceae, Ruminococcaceae,* and *Rikenellaceae* is associated with T1D protection, leading to T1D improvement [129].

Mucosal-associated invariant T cells (MAIT) are innate-like lymphocytes that protect from bacterial infections. These cells have been linked to beta-cell damage. Therefore, MAIT cells may have a role in the occurrence of T1D. They further proposed that MAIT cells enhance gut permeability, which modulates the translocation of bacteria metabolites to systematic circulation. As a result, the bacterial components contribute to the development of T1D by activating dendritic cells in the pancreatic lymph node (PLN) and boosting anti-islet T cell responses [129]. It is supposed that the reaction of antibodies against β-casein may be related to autoimmune diabetes because elevated titers of anti- β-casein have been detected by the new diagnosis of T1D and latent autoimmune diabetes (LADA) [125].

The presence of coeliac disease (CD) in T1D patients is very common and is also related to poor glycemic control and lipid profiles. Coeliac disease is a disorder when the immune system attacks the tissue due to gluten consumption. Gluten influences Gut homoeostasis, as it increases intestinal permeability by affecting tight junctions. Thus, long gliadin peptides can penetrate the lamina propria and translocate into other sites, such as pancreatic lymph nodes, activating autoreactive T cells. It was found that there was a low T-cell response against gliadin in newly diagnosed T1D children compared to healthy controls and children with longer T1D. This observation proves the development of T1D is due to aberrant immune response [125].

GABA is a metabolite from glutamate as a cellular response to acidic stress by several lactic acid bacteria's glutamate decarboxylase (GAD) pathway. GABA is the primary inhibitory neurotransmitter in the enteric and parasympathetic nervous systems, especially in pain perception and stress. GABA, on the other hand, has been postulated as a possible treatment in the pathophysiology of T1D. GABA activates β-cell receptors, increasing insulin synthesis and proliferation while decreasing apoptosis. Furthermore, GABA has been found in CD4+ T cells, reducing the inflammatory process associated with the pathogenesis of T1D [123].

A lower abundance of *Actinobacteria, Firmicutes* and a lower ratio of *Firmicutes* to *Bacteroidetes* have been observed in children with T1D than in non-diabetic children. In addition, a high abundance of *Clostridium, Bacteroides,* and *Veillonella* have been detected in T1D children. Like T2D, insufficient butyrate-producing bacteria and low bacteria diversity has been found. Another study showed that *Lactobacillus reuteri* increases insulin secretion and improves glucose tolerance [123], [129].

7.3.3. Metformin

Metformin is the most often used oral diabetes treatment. Metformin inhibits hepatic glucose synthesis, decreases intestinal glucose absorption, and improves insulin sensitivity by boosting peripheral glucose uptake and utilization. Metformin also functions as an insulin hormone modulator, increasing GLP-1 levels in the gut. It can inhibit fat absorption and LPS-induced inflammation. A recent study found a significant abundance of *Turicibacter* and *Spirochaete* among metformin patients [6].

The abundance of *A. muciniphila* has increased after the treatment with metformin in diabetic patients who suffer from glycemia and low abundance of *A. muciniphila.* It has been observed that metformin altered the Gut microbiota functions, such as intestinal lipid

absorption and LPS-stimulated inflammation. Interesting, a similar abundance of *Akkermansia* has been observed in non-diabetic people and patients who take metformin [123]. Because metformin changes the gut microbiota composition, a low abundance of *Bacteroides,* especially *Bacteroides fragilis*, has been observed [127]. Metformin has a half-life of roughly 3-4 hours; however, its impact lasts longer than its half-life. In addition, the effect of the same dose's dosage type, whether delayed-release or extended-release, is identical. Furthermore, intravenous metformin treatment is not as successful as oral metformin administration in controlling blood glucose levels [130]. Therefore, the efficacy of this medication may be because of its action in the gut [127]. Metformin also modulates the bile acid, which doesn´t only regulate cholesterol synthesis, but also affects glucose hemostasis [127].

Metformin's gut flora changes cause gastrointestinal intolerance, a typical adverse effect. This adverse effect might be caused by *Escherichia*, as this species has been linked to gas production in diabetic individuals using metformin [130].

7.3.4. The complication of diabetes

Diabetes retinopathy is a common complication of diabetes caused by high blood sugar levels that damage the blood vessels of light-sensitive tissue in the retina. The specific mechanism of retinopathy is unknown. According to research, the ocular surface includes around 12 kinds of bacteria. These bacteria included *Corynebacterium*, coagulase-negative *Staphylococci*, *Acinetobacter* spp., and dangerous bacteria such as *Pseudomonas*. The relationship between gut microbiota and diabetic retinopathy is currently being researched [122], [124].

Another complication of diabetes is diabetic neuropathy. It is a nerve injury caused by high blood sugar levels, which causes demyelination, axon atrophies, and inflammation. Neuropathy can manifest itself in the gastrointestinal (GI) tract. It affects numerous regions of the gastrointestinal system, producing constipation or diarrhea, stomach pain, nausea, and, in rare cases, vomiting. In addition, because diabetes causes low-grade inflammation, LPS and CD14 or peptidoglycan have a role in influencing neuronal homeostasis. Furthermore, myenteric neurons play an essential role in GI motility by signaling smooth muscle and coordinating movement at various sections of the GI tract. Dysmotility is caused by apoptosis or necrosis of myenteric inhibitory motor neurons. Neuropil rearrangement, cytoskeletal

filament loss, and axonal swelling result from the damage. The link between dysbiosis and diabetic neuropathy is also unclear [122].

Another complication of diabetes is diabetic nephropathy, characterized by a poor glomerular filtration rate and increased albuminuria. One of the primary causes of diabetic nephropathy is increased renin-angiotensin system (RAS) activation. The activation of the GLP-1/GLP-1 receptor complex reduces proximal tubular reabsorption and expansion, hence alleviating the early symptoms of diabetic nephropathy. SCFAs bind to GPCRs and an olfactory receptor (Olfr78). The smooth muscles present in the renal arteries mainly express GPR41 and Olfr78. The propionic acid produced by the intestinal flora that binds to the Olfr68 can activate intrarenal RAS. This process raises glomerular and systemic pressure, which can contribute to the development of Diabetic nephropathy. Some studies have recently attempted to grasp the consequences of phenyl sulfate (PS) in diabetic nephropathy. PS is classified as a uremic toxin generated from gut microbiota. It is linked to early kidney damage in diabetic patients, making it a promising potential diagnosis for identifying people with diabetes at risk of developing Diabetic nephropathy. Furthermore, its participation in several molecular pathways contributing to podocyte damage. It suggests that blocking PS synthesis might be a viable pharmacological strategy. Butyrate strengthens the intestinal barrier, lowering LPS and TMAO translocation in the bloodstream and preventing renal function loss [122].

7.3.5. The possible treatment of diabetes

Lactobacillus spp., Enterococcus spp., Bifidobacterium spp., and *Streptococcus spp.* are the most often utilized probiotics. Another RCT demonstrated the effectiveness of *L. reuteri* by increasing GLP-1 and insulin secretion while not affect insulin sensitivity[120], [124], [125]. Butyrate-producing bacteria, such as *R.intestinalis, Lactobacillus rhamnosus* GG, *Faecalibacterium* spp., and *Eubacterium hallii,* can be possible options as probiotics for the treatment of diabetes [123]. A study proved the antidiabetic effect of administration of probiotic, such as Lactobacillus *acidophilus, Streptococcus thermophilus, L. bulgaricus* and/or *Bifidobacterium lactis*. In addition, *Bifidobacterium animalis, Bifidobacterium longum*, and *Bifidobacterium breve* were used to treat glucose intolerance [122].

Symbiotics derived from the combination of probiotics (animal *Bifidobacterium* milk subspecies DSM10140 and *Lactobacillus paracasei* DSM46331) and prebiotics (oat -glucan)

dramatically decreased weight gain, blood glucose and blood lipids and changed intestinal homeostasis [124].

Berberine is an herbal preparation that has anti-inflammatory and antioxidant effects. It has been demonstrated that it has a hypoglycemic effect on T2D patients by decreasing intestinal glucose absorption and enhancing insulin sensitivity. Furthermore, altering the expression of peroxisome proliferator-activated receptors stimulates insulin secretion and alters glucidic metabolism at the hepatic level [122], [125].

The effect of DPP-4i on the microbiota might be linked to an increase in GLP-2's intestinotrophic action, which raises the integrity of the intestinal mucosal barrier and hence reduces permeability [120].

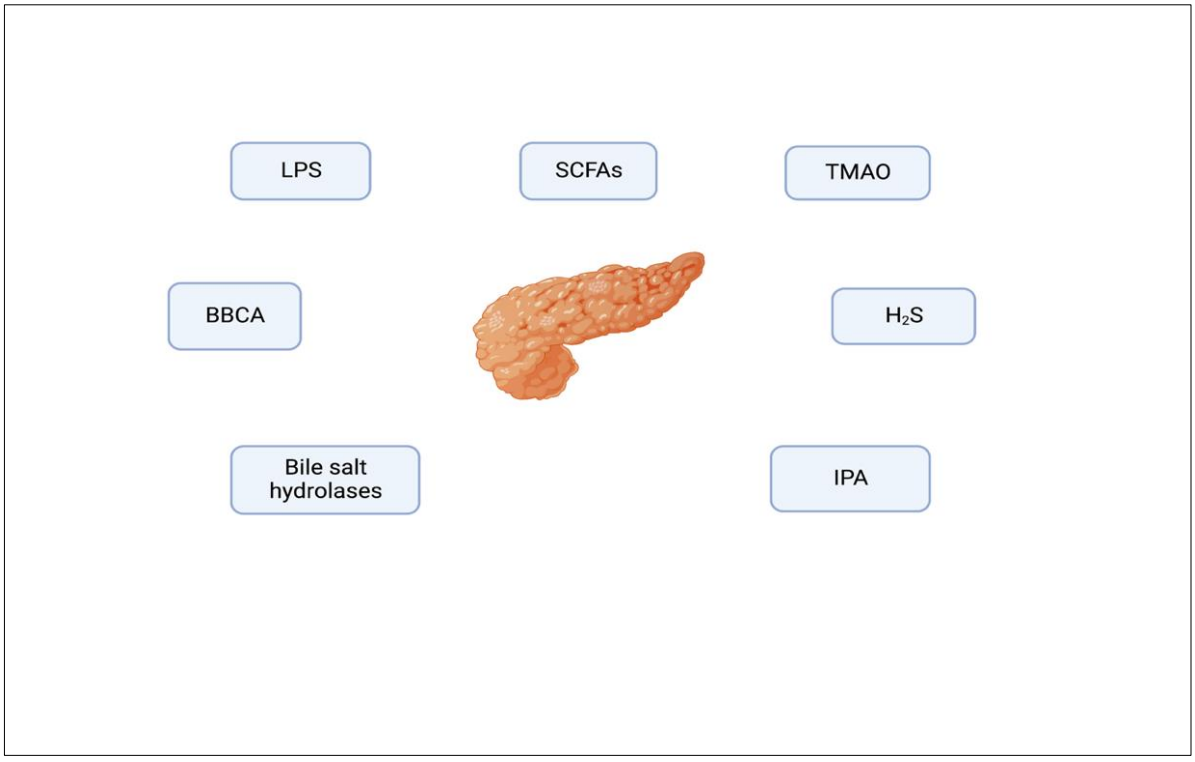

Figure 4. Schema indicates the bacterial metabolites and mediators, which affect the pathogenesis of T2D [122].

8. Altered Gut- Brain axis in respiratory diseases

8.1. Asthma

Asthma is the most frequent chronic condition among children and a primary noncommunicable disease (NCD). Asthma symptoms are caused by inflammation and constriction of the tiny airways in the lungs, which can include any combination of coughing, wheezing, shortness of breath, and chest tightness.

Upper airway microorganisms begin at birth when the respiratory tract (e.g., naso- and oropharynx) gets the bacteria during delivery. The colonization of microorganisms differs and depends on the delivery, with infants delivered vaginally having a distinct composition of microbes than those born through the Caesarian section. After birth, the respiratory microbial population continues for the first two years of life, with *Dolosigranulum* and *Moraxella* species forming a persistent nasopharyngeal bacterial environment. Also, other factors change the nasopharyngeal microbiota, such as environmental factors, breastfeeding, viral infection, and antibiotic administration [131]–[134].

The epithelial mucosa and dendritic cells are in constant touch with the airway lumen and antimicrobial peptides generated by immune cells. All of this has significant roles in response to environmental chemicals. The epithelium regulates the local immunological activities of IgA antibodies, defensins, and lysozymes, which are also influenced by IL-25, IL-33, and thymic stromal production lymphopoietin (TSLP), all of which increase Th2 inflammation, resulting in causing Asthma. A recent study found that treatment with an anti-TSLP antibody reduced allergen-induced bronchoconstriction and decreased indicators of Th2-related airway inflammation, such as the amount of exhaled nitric oxide and the number of eosinophils in the sputum. Other cytokines that epithelial cells produce include IL-10 and transforming growth factor (TGF)-β. This Mechanism suggests that the airway epithelium plays a crucial role in coordinating innate and adaptive immunity in the development of asthma. In addition to muco-ciliary clearance, airway mucus has additional important features in asthma. Dendritic cells (DCs) deliver microbe fragments to the immune system, stimulating various regulatory and adaptive responses, including Th1, Th2, and Th17 pathways. DCs may activate various immune cell types, including T cells and innate lymphoid cells (ILCs), which are a kind of cells found at barrier surfaces that can offer environmental cues that also target commensal bacteria [131], [132], [134], [135] . The involvement of iNKT cells in asthma etiology is yet unknown [131]. Respiratory infections stimulate the Th17 response, which

causes intestine damage. All of these demonstrate a relationship between changed gut microbiota and the prevalence of Asthma [131]. In asthmatic children, peripheral blood levels of inflammatory factors such as C-reactive protein, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are elevated [135].

Another molecule discovered to have a favorable effect on the immune system is N-glycolylneuraminic acid (Neu5Gc), a sialic acid generated by non-human mammalian cells but not by bacteria or humans. Children with higher levels of anti-Neu5Gc-IgG antibodies were more likely to grow up on a farm and were less likely to suffer from wheeze and asthma [136].

The form and function of inducible bronchus-associated lymphoid tissue (iBALT) and gut-associated lymphoid tissue (GALT), which both are part of the mucosal-associated lymphoid tissue, are similar. GALT and iBALT modulate IgA synthesis and secretion at mucosal surfaces, as well as Th cell and cytotoxic (Tc) responses. Local immunity is regulated in Peyer's patches with the help of GALT and mesenteric lymph nodes. The proliferation of B cells into plasma cells leads to secreting antibodies in the lamina propria. In the lamina propria, many memory and effector T and B cells exist. In adulthood, gut mucosal tissue contains 80% of active B lymphocytes [137]. The epithelium regulates local respiratory and immune activities, which are also regulated by thymic stromal lymphopoietin, IL-25, and IL-33, and may result in Th2 inflammation, favoring asthma development. According to one research, induced Tregs (iTreg) are Tregs created in the periphery (rather than the thymus). They are primarily triggered in the mesenteric lymph nodes (MLN), Peyer's patches, and the lamina propria (LP) of the small and large intestines [131], [132], [135]. The first 100 days of life, known as the critical window, are vital for bacterial growth and developing IgE-mediated hypersensitivities in humans [131], [132].

Early viral infections, primarily caused by rhinovirus or respiratory syncytial virus (RSV), have also been associated with asthma development. Furthermore, colonization with *Streptococcus pneumoniae, Moraxella catarrhalis,* or *Haemophilus influenza* at one month of age has been related to an increased risk of asthma development and heightened Th2-associated response [131], [132], [134], [136]. By regulating secreted metabolites, such as elevated level of IL-10 and low level of IL-12, *Akkermansia muciniphila and Faecalibacterium prausnitzii* can suppress inflammation. As a result, these bacteria have been found in low concentrations in asthmatic patients [135]. Changes in the lung microbiota alter steroid responsiveness and the expression of the eosinophilic inflammation Th17 gene [131].

Neutrophilic inflammation in asthmatics may also be related to airway microbiome components. Neutrophilic asthma is a subtype with a different immunopathogenesis than

allergic or eosinophilic asthma and is often more challenging to treat. Neutrophil abundance in asthmatic sputum has been related to levels of specific taxa, including *Moraxella* [131].

Furthermore, *Clostridia* have been demonstrated to induce ILC3s to create IL-22, which helps to maintain the epithelial barrier and lowers intestinal permeability to dietary proteins. *Bifidobacteria* and *Lactobacilli* can boost the production of T regulatory cells by stimulating metabolic processes in dendritic cells, such as vitamin A metabolism, tryptophan metabolism, and heme oxygenase 1. A *Bifidobacterium longum* exopolysaccharide has recently decreased Th17 responses in the gut and the lung [138]. The potential of *Haemophilus parainfluenzae* to activate Toll-like receptor (TLR) 4 has been documented, which generates various pro-inflammatory cytokines such as IL-8 and inhibits corticosteroid-related pathways. As a result, it is proposed as a cause of the development of corticosteroid resistance [136].

Bacteria microbiotas differ in Asthma patients than in healthy patients. Relative abundance of *Lachnospira* and low abundance of *Veillonella, Faecalibacterium,* and *Rothia* have been observed in children at risk of asthma. Decreased these bacteria were associated with a low level of fecal acetate and dysregulation of enterohepatic metabolites. Other studies showed a high abundance of *Clostridium* spp. in children at high risk [131], [132], [136]–[138]. Low abundance of *Bifidobacterium, Akkermansia, Faecalibacterium,* and *Ruminococcus gnavus,* as well as a high abundance of *Candida* and *Rhodotorula* in small children, indicate an increased risk of developing allergic diseases, especially Asthma [131], [137]– [139]. Furthermore, enrichment of *Proteobacteria* in asthmatic patients has been detected [133]. In addition, it has been shown that histamine-producing bacteria are more prevalent in the feces of asthmatic patients than in non-asthmatic individuals [137]. In treatment-resistance asthmatic patients, enrichment of *M.catarrhalis, Haemophilus* spp., and *Streptococcus* spp. are linked with worse lung function and high levels of IL-8 and neutrophil [140]. Increased abundance of *Haemophilus* and *Moraxella* and low abundance of *Streptococcus, Gemella,* and *Porphyromonas* have been detected in patients with eosinophilic asthma who inhaled high doses of corticosteroids (ICSs). Enrichment of *Klebsiella* was reported in patients with severe asthma [137], [138]. Increased abundance of *Proteobacteria* and *Pseudomonas* and decreased abundance of *Bacteroidetes, Fusobacteria,* and *Prevotella* have been associated with the treatment with the combination of inhaled and oral CS [137]. Fungal components such as mannans, proteases, chitin, and β-glucans are frequently found in everyday human allergens and home dust; hence changed fungal populations in the lungs of asthmatic patients are not unusual. Even though the underlying sensitization processes are unknown, many people with severe and/or uncontrolled asthma are sensitive to fungus [137]. RSV increases the severity of

asthma, whereas influenza is associated with asthma aggravation. It has been proposed that IL-33 causes influenza-induced asthma exacerbation [136], [137].

In asthmatic children, combining nutritional supplements such as fish oil and vegetable extract with probiotics improves pulmonary function and reduces the usage of short-acting inhaled bronchodilators and inhaled corticosteroids [138]. Furthermore, probiotics can help with asthma. In asthmatic children, *Lactobacillus acidophilus* and *Bifidobacterium animalis* administration reduce fever, cough, and antibiotic usage [136], [139], [140]. The administration of *Lactobacillus rhamnosus* improves asthma prophylaxis. Furthermore, taking a capsule containing *Lactobacillus paracasei* and *Lactobacillus fermentum* improved lung function and reduced IgE levels [136].

8.2. COVID 19

Covid 19 is a mild to severe respiratory infection caused by severe acute respiratory syndrome coronavirus 2 of the genus Beta coronavirus (SARS-Cov-2). It is spread primarily through contact with infectious material (such as respiratory droplets), or objects or surfaces contaminated with the causative virus. It is characterized by fever, cough, and shortness of breath. It can progress to pneumonia and respiratory failure.

The early stage, immediately after infection, is characterized by a high viral load and decreased inflammatory activity, with few symptoms and is also linked with gastrointestinal sicknesses, such as diarrhea, loss of appetite, nausea, and vomiting. COVID-19-positive persons suffer the most severe symptoms, such as respiratory difficulties and fever, during the late phase of infection. Immune cells such as neutrophils, activating monocytes, and macrophages produce inflammatory cytokines and reactive oxygen species. In addition, respiratory signs such as cough, sputum production, and shortness of breath continue to be the most prevalent symptoms after fever or pneumonia. Elevated levels of IL-6 and IL-10 have been linked to the severity of the illness. A greater cytokine storm syndrome level is related to consequences such as acute respiratory distress syndrome or septic shock [12], [141].

The gut microbiota influences the development of type I interferon receptors in respiratory epithelial cells, which respond quickly to viral infections by secreting IFN-α and IFN-β, limiting viral replication. The antibiotic effect of gram-positive gut bacteria impairs the distribution or activation of dendritic cells from the respiratory tract. It causes a decrease in DC migration from the lung to the draining lymph nodes. Furthermore, the intestinal microbiota

can activate specific CD4+ and CD8+ T lymphocytes and stabilize the expression of pro-IL-1 β, pro-IL-18, and NLRP3 after a viral load. At the same time, inflammasome activation promotes the maturation and migration of DCs from the lungs to the draining lymph nodes. Gut microbiotas have been found to influence the lung mucosa by generating antiviral effects in epithelial or innate immune cells and reducing viral multiplication at the beginning of an infection. Because of cellular and humoral adaptive responses, innate immunity improves in the late stages of the disease [141]. Beneficial bacteria regulate the balance of inflammatory regulatory T cells (Treg) and pro-inflammatory responses like Th17. Gut bacteria play an important role in immune system maintenance. The immune system identifies SARS-Cov-2 through molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs) with the aid of Toll-like receptors (TLRs) and nucleotide-binding receptors (NBRs) (NODs). As a result, the immune system reacts to the infection. Metabolites and immunomodulatory signals are produced by gut microbiota. SCFAs such as butyrate, acetate, propionate, and secondary bile acids can attach to the surface receptors of DCs and macrophages, influencing their activities and breakdown. *Bifidobacterium lactis* can increase leukocyte counts and NK cell tumoricidal activity [141]–[143]. Gut dysbiosis is linked to higher mortality risk in respiratory infections because it is considered to raise the levels of INF- γ, IL-6, and CCL2, as well as decrease regulatory T cells in the lung and GIT [141]. COVID-19 patients with elevated levels of pro-inflammatory cytokines and chemokines such as Granulocyte-colony stimulating factor (G-CSF), the human interferon-inducible protein 10 (IP-10/CXCL10), monocyte chemoattractant protein 1 (MCP-1) and tumor necrosis factor-alpha (TNF-α), as well as T helper 2 cell cytokines such as interleukin (IL)-4 and IL-10 [144], [145].

Gastrointestinal symptoms are caused by a change in gut microbiota and a lack of intestinal barrier integrity. Another marker for disease surveillance is calprotectin. Diarrhea might be caused by inflammatory cells entering the intestinal mucosa and affecting the gut microbial environment. The gut microbiotas influence pro-inflammatory cytokines, increasing systemic inflammation [12]. Infected individuals have Covid virus in their esophagus, stomach, duodenum, and rectal [141]. The gut microbiotas employ a variety of cells, primarily antigen-presenting cells such as dendritic cells in the Peyer's patches of the intestine, Langerhans cells, and macrophages. In addition, Mast cells and Natural Killer cells interact with the gut microbiota [143].

SARS-CoV-2 penetrates cells through its protein S binding to the infected cells' Angiotensin-Converting Enzyme II (ACE2) receptors. As we know, ACE2 plays a critical role in the conversion of angiotensin I to angiotensin II, modulating vascular homeostasis,

vasomotor tone, and blood pressure regulation. ACE2 receptors are expressed in various human cells vulnerable to viral infection, including epithelial cells in the lungs, small intestine and colon, kidney tubular cells, neuronal and glial cells in the brain, enterocytes, vascular endothelial cells, smooth muscle cells, and cardiomyocytes. SARS-CoV-2 also employs transmembrane protease serine 2 (TMRPSS2) receptors, an enzyme presents in small intestinal epithelial cells, to enter infected cell [12], [141], [143]–[145]. The virus may trigger ACE2 receptors in the gut, increasing intestinal inflammation and diarrhea vulnerability. The co-expression of ACE2 and TMPRSS2 was reported to be high in enterocytes, esophagus, and lungs. ACE2 receptors don´t play an essential role in intestinal inflammation, but they also influence the intestinal microbiota [12], [141]. During the infection, a link between the ACE2 transporter and the gut microbiota was discovered [12]. ACE2 regulates the expression of the amino acid transporter B0AT1, which controls the intestinal absorption of tryptophan. Tryptophan regulates the mRNA expression of antimicrobial peptides via the mTOR pathway, and antimicrobial peptides may alter the gut microbiota composition. ACE2 downregulation leads to a reduction of intestinal absorption of tryptophan. Therefore, the release of antimicrobial peptides decreased, and pathogen survival and gut dysbiosis increased. Antimicrobial peptides act as virolytic agents, preventing viral fusion in the host cell or replication. Anti-coronavirus peptides inhibit virus-host cell fusion in SARS-Cov-2 by inhibiting HR1 and HR2 from forming a fusion-active core or cleaving the S protein [143], [145]. Many studies have shown that ACE2 receptors function in inflammation; however, ACE2 blockers ameliorate cardiovascular disease. ACE2 blockers in hypertension showed decreased covid 19 comorbidities [12]. SARS-CoV-2 might potentially upregulate RAS in cardiovascular patients and deplete ACE2. The low ACE2 levels in tissues have been linked to viral replication efficiency and pathogenicity, altering RAS. RAS-ACE2 imbalance may worsen tissue inflammation and strength of COVID-19 symptoms in individuals with pre-existing cardiovascular disease and other comorbidities. ACE2 receptors may be a target for COVID-19 therapies in individuals with a high cardiovascular risk. However, inhibition of ACE2-protective effects following SARS-CoV-2 infection due to ACE2 depletion is highly likely to maintain the poor outcomes found in COVID-19 patients, particularly those with pre-existing diseases [12], [143]. Obese patients have increased amounts of ACE2 receptors in their adipocytes. As a result, reducing or eradicating inflammatory adipose tissue may be associated with diminished viral impact. Obese people have higher pro-inflammatory adipokines, leukotrienes, and chemerin [12].

Enrichment of *Ruminococcus gnavus* has been found in COVID-19 patients, whereas a low abundance of *Colistridia* was detected. The high abundance of *Coprobacillus, Clostridium ramosum,* and *Clostridium hathewayi* and the low abundance of *Faecalibacterium prausnitzii* were related to the infection´s severity. Furthermore, *Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis,* and *Morganella morganii* have increased in the fecal culture of covid patients. In contrast, increased abundance of SCFAs -producing bacteria, such as *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii, and Lachnospiraceae bacterium* in low- to infected people [12], [141], [143], [145]. It has been reported in a study with Covid patients in comparison with HINI patients and healthy participants that there is a low abundance of *Actinomyces, Rothia, Streptococcus, Veillonella,* and *Bifidobacterium* genera. Another study showed enrichment of fungi, such as *Candida albicans, C. auris, Aspergillus flavus* and *A. nigra* [141], [143], [145].

Covid 19 is treated using non-steroid anti-inflammatory medications. Although paracetamol does not affect the makeup of the gut microbiota, its absorption rises when dysbiosis is activated. Glucocorticoids, another Covid therapy option, have been shown to change gut microbes. Furthermore, Remdesivir does not affect microbiota; nevertheless, when taken with doxycycline, hydroxychloroquine, which is not indicated for treatment against SARS-CoV-2, has been observed to influence microbial community composition [145].

A low-fat diet was shown to enhance *Bifidobacterium* abundance, whereas a high saturated fat diet was found to promote *Faecalibacterium prausnitzii* enrichment. The consumption of butylated high amylose maize starch enhanced plasma levels of the anti-inflammatory cytokine IL10. It can improve SCFA synthesis and strengthen gastro-intestinal related lymphoid tissue (GALT). A fiber-rich diet not only modifies the intestinal microbiota but can also affect the lung microbiota, showing the role of nutrition on lung immunity. Probiotics are found in fermented foods, such as cultured milk products and yoghurt. Yoghurt-containing probiotics have been shown to lower the numbers of the entomopathogens *E. coli* and *Helicobacter pylori*. Probiotics have shown promising outcomes in reducing inflammation and modulating innate immunity via toll-like receptors and the accompanying signaling pathways [142], [143], [145]. The production of antibodies necessitates a high protein intake. Infection risk has also been related to a deficiency of vitamin A or zinc. Branched-chain amino acids can improve the intestinal barrier by increasing immunoglobulin levels. Omega-3 fatty acids, as well as vitamin C, vitamin E, and phytochemicals present in plant-based diets, such as carotenoids and polyphenols, have powerful anti-inflammatory and antioxidant properties. Numerous investigations have discovered a link between vitamin D levels in the immune

response to infection and the severity of COVID-19 responses and mortality [12], [145]. As usual, the probiotic *Lactobacillus rhamnosus* GG reduces the diarrhea duration and hospitalization for covid patients. The probiotic formulation contained *Lactobacillus acidophilus, L. helveticus, L. paracasei, L. plantarum, L. brevis, Bifidobacterium lactis*, and *Streptococcus thermophilus* to improve the symptoms and stop diarrhea in covid patients [141], [143]–[145]. Many hospitals use the probiotics, such as the medical university of Graz in Austria. They suggested the symbiotic oral treatment with *Bifidobacterium bifidum, B. lactis, Enterococcus faecium, Lactobacillus acidophilus, L. paracasei, L. plantarum, L. rhamnosus, L. salivarius,* inulin, and fructo-oligosaccharide (FOS), may reduce the duration of diarrhea and improve the stool consistency and the gastrointestinal symptoms [141].

9. Role of Gut- Brain axis in cancer

The gut microbiotas play an essential role in cancer development and treatment. Toxic metabolites or cancerogenic products secreted by gut microbiota can either act as cancer-transforming agents or indirectly cause cancer by promoting inflammation or immunosuppression. Furthermore, the limited therapeutic effect is due to gut microbiome disturbance [146].

The intestinal mucosa consists of a single epithelial cell layer comprised of intestinal epithelial cells (IECs) and intraepithelial lymphocytes. This distinct structure encourages interaction with the immune system. Paneth and goblet cells are found in IECs and secrete antimicrobial peptides and mucus, which coat the epithelium. The lamina propria is a connective tissue layer that lies underneath the mucosal layer and contains Peyer's patches as well as antigen-presenting cells (APCs), innate lymphoid cells, and T and B cells. This lymphoid tissue associated with the intestine plays an essential role in local and systemic immunological responses. Pattern recognition receptor-mediated identification of pathogen-associated molecular patterns (PAMPs) promotes local immunity. PRRs include Toll-like receptors (TLRs) on IECs and innate immune effectors in the gut, whereas PAMPs include lipopolysaccharide and flagellin. Furthermore, metabolites produced by bacteria, primarily through synthesizing SCFAs, might alter local immune responses. The draining lymph nodes of the gut are called mesenteric lymph nodes because they are found in the mesentery of the small intestine and colon (mLNs). The gut bacteria modulate the adaptive immune responses within the mLNs and consequently influence the development of naïve T cells. PAMPs

stimulate APC maturation, especially in dendritic cells (DCs). When DCs mature, they reach the mLNs, where they communicate with and support the development of naïve T cells into CD4+ T cells, notably CD4+ T regulatory cells (Tregs) and T helper 17 (Th17) cells, leading to modulating the intestinal tendency. Activated T cells play an essential role in intestinal homeostasis, as indicated by Tregs-induced mucosal tolerance and the production of immunosuppressive cytokines, such as IL-10. It is worth noting that constant interaction occurs between intestinal symbionts and mucosal T cells because bacterial metabolites such as SCFAs enhance the intestinal maintenance of these cells. The ability of SCFAs to decrease histone deacetylase activity indicates the presence of epigenetic control. Alternatively, Treg formation is mediated through a route involving polysaccharide A and TLR signaling to DCs. Th17 cells, a specific subset of CD4+ cells, are present in the gut lamina propria and play an important role in pathogen infection prevention. Th17 cells have a role in mucosal immunity because cytokines released by Th17 cells, such as IL-17, encourage IECs to form tight junctions and secrete antimicrobial proteins. Other inflammatory cytokines can be released because of IL-17. Neutrophils can also be recruited from the bloodstream to the intestinal microenvironment. Immune cell priming mediated by the microbiota can influence systemic immune responses. When DCs deliver gut bacteria antigens in the mLNs of the gut, B cells and T cells, including Tregs and Th17 cells, can move throughout the body and induce immune responses against identical foreign antigens or different antigens by cross-reacting with similar epitopes. Th17 cells are functionally flexible in that they may change their cytokine production based on whether the environment is inflammatory or non-inflammatory [146]–[149].

Dysbiosis disrupts the intestinal barrier, allowing germs to translocate into mLNs and enter the peripheral circulation. Thus, Th17 and effector T cells are activated, resulting in the influx of neutrophils and the propagation of inflammation locally and across the body[146], [147]. *Fusobacterium nucleatum* suppresses host Natural Killer (NK) cells to attract myeloid suppressor cells at the site of infection, indirectly aiding cancer development. This method is mediated by the bacterial virulence factor Fap2, which can bind and block the NK inhibitory receptor TGIT, hence halting NK-driven tumor cell assault [149], [150].

Polyamines, microbial metabolites, decrease anticancer immunity by reducing lymphocyte proliferation and promoting the production of tumor-derived proteases, which increases tumor cell invasiveness. Lipoteichoic acid (LTA), generated from Gram-positive bacteria, increased tumor burden in individuals with obesity-associated HCC by translocating to the liver. In conjunction with the bacterial metabolite deoxycholic acid, LTA causes a senescence-associated secretory phenotype, upregulating cytochrome C oxidase subunit 2 (COX2)

expression via TLR2-mediated signaling. Following prostaglandin E2 (PGE2) synthesis mediated by COX2, anti-tumor immunity is inhibited via the prostaglandin E receptor 4 (PTGER4) [148].

H. pylori has been observed to promote tumorigenesis by activating the β-catenin signaling pathway. In contrast, eradicating *H. pylori* decreases the risk of gastric Cancer in infected patients. H. pylori and interleukin-22 (IL-22) activate the extracellular signal-regulated kinase (ERK) pathway in gastric epithelial cells, causing MMP-10 to be produced. MMP-10 not only causes inflammation by producing chemokine ligand 16 (CXCL16) and recruiting CD8+ T cells, but it also causes damage to the gastric mucosa by blocking tight junction proteins [150]–[152]. *Bacteroides fragilis, Fusobacterium nucleatum, Porphyromonas asaccharolytica, Parvimonas micra, Prevotella intermedia, Alistipes finegoldii*, and *Thermanaerovibrio acidaminovorans* were found in fecal metagenomic samples from colorectal cancer CRC patients. They could potentially serve as diagnostic bacterial markers across populations. The relationship between CRC-enriched bacteria and several processes, including lipopolysaccharide and energy production. Catabolism of protein and mucin, as well as carbohydrate breakdown, gives insight into their functional capability in (CRC) [151], [153]. *Fusobacterium nucleatum* has been widely researched in Colorectal Cancer. Through its Fap2 protein, *F. nucleatum* may promote intestinal tumorigenesis by sticking to cancer cells and regulating immune cells. The bacteria might alter the tumor microenvironment, activate the β-catenin cancer pathway, and stimulate the production of microRNA-21. Aside from primary cancer growth, *F. nucleatum* may also trigger Toll-like receptor 4 (TLR4) to activate various microRNAs and autophagic pathways, altering patients' chemotherapy responses. Furthermore, a recent study linked *Fusobacterium* to colorectal cancer metastasis by detecting live *Fusobacterium* in distant metastatic lesions [148], [153]. Oral microbiota, such as *porphyromonas gingivalis,* were linked with a high risk of pancreatic Cancer [153].

During the treatment with chemotherapy, the delicate process by which the microbiome might improve the anticancer immune response induced by treatment may differ. Cyclophosphamide, for example, caused the translocation of *Enterococcus hirae* and *Lactobacillus johnsonii* into mLNs, enhancing the response of Th17 in the spleen and activating memory Th17 response, besides the accumulation of *Barnesiella intestinihominis* in the colon. Both bacteria can control the immunological activation in anti-tumor immunity, accompanied with increased the upper gastrointestinal permeability [146], [147], [151], [153], [154].

Radiotherapy has a powerful immunological modulatory impact by presenting tumor-associated antigens to cytolytic CD8+ T cells and IFN- γ [151].

In patients with CRC, who were given probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium lactis*, it was discovered that they had an increased abundance of butyrate-producing bacteria (particularly *Faecalibacterium* and other *Clostridiales*) within the tumor. Another study examined pre-operative probiotic therapy's effect on CRC patients' mucosal immunity, revealing altered cytokine profiles within the colonic mucosa at the time of colon resection. It was a lower IL-1b, IL-10, and IL-23A mRNA levels in probiotic-treated patients compared to controls who did not receive probiotics [147], [151]. Furthermore, during radiotherapy, the probiotics modulate the host inflammation, affecting the efficacy of radiotherapy [151]. Probiotics have been proven to aid in the prevention of radiation-induced enteropathy. Preparations comprising *Bifidum, Lactobacillus casei, Streptococcus, Lactobacillus*, Bifidobacterium spp., and the VSL#3 formulation including *Streptococcus, Lactobacillus*, and *Bifidobacterium* spp., have been shown to prevent radiation-induced gastrointestinal toxicity, such as diarrhea [154].

Febrile neutropenia (FN) is a serious treatment-related complication that can be fatal in cancer patients receiving severe chemotherapy. The endogenous flora is a significant source of infection during neutropenia. According to existing human research, probiotics not only reduce the degree of enrichment of harmful bacteria invading the gut, but they may also shorten the duration of neutropenia. Although many studies have indicated that probiotic medication is helpful, proof of probiotic safety is still lacking, particularly in immunocompromised individuals. This new study will look at the safety and efficacy of probiotics in cancer treatment [154].

The gut microbiotas are crucial in patients treated with immune checkpoint blockade. Overall survival and progression-free survival rates with anti-PD-1/PD-L1 therapy were considerably more significant in epithelial tumor patients who did not get antibiotics for routine purposes than in tumor patients who received antibiotics. This finding suggests that antibiotic usage may disrupt the gut microbiota, affecting anti-tumor immunity and the response to immune checkpoint inhibition. The efficacy of anti-PD-1 therapy in patients with metastatic melanoma was also influenced by gut microbiota. The variety of gut microbiota was dramatically enhanced in patients responding to PD-1 treatment, and some bacteria, such as *Clostridiales, Ruminococcaceae*, and *Faecalibacterium*, were comparatively more prevalent. Non-responding patients, on the other hand, showed a lesser variety of gut bacteria and a more significant abundance of *Bacteroidales* [146], [147], [150], [153]. The observations in patients

show that CTLA-4 antibody effectiveness is linked to T cell responses caused by *B. fragilis* or *Bacteroides thetaiotaomicron.* Furthermore, *Bifidobacterium breve* and *Bifidobacterium longum* have been shown to improve dendritic cell activity and, as a result, stimulate CD8+ T cell priming and accumulation in the tumor microenvironment [151]. Patients with melanoma who received anti-CTLA-4 therapy and were rich in *Bacteroidetes* and several genetic pathways of polyamine transport and B vitamin production did not develop colitis. This type of toxicity might be linked to the known effects of these bacteria on Treg differentiation. Other studies have found that patients with greater *Faecalibacterium prausnitzii* abundance and lower *Bacteroides* abundance following anti-CTLA-4 medication had a higher risk of colitis [146], [147], [150], [151], [154]. Non-responders to treatment with PD-1 blockade had lower levels of *Akkermansia muciniphila*. This observation has been shown to promote the recruitment of CCR9+CXCR3+CD4+ T lymphocytes to the tumor microenvironment via the IL-12 pathway in fecal samples from patients with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) [148], [151], [154].

A study detected that the low abundance of *B. fragilis* and high abundance of *Bacteroidales* prevent the effect of anti-CTLA-4 in metastatic melanoma patients. In addition, another study found a higher ratio of *B. fragilis* leads to tumor regression. In addition, butyrate-producing bacteria, such as the *Faecalibacterium* genus and *G. formicilis,* were linked to longer-progression-free survival (PFS) and overall survival (OS) [146].

CpG oligonucleotides (CpG-ON) are TLR9 ligands on immune cells that boost the immune response to cancer cells and generate an anti-cancer effect. The impact of CpG-ON was amplified when patients were given IL-10 receptor antibodies to counteract the immunosuppressive effects of tumor-infiltrating Treg cells. CpG-ONs stimulate myeloid cells to produce pro-inflammatory cytokines such as TNF and IL-12. TNF and IL-12 stimulate macrophage and dendritic cell infiltration, producing a pro-inflammatory state and fast hemorrhagic necrosis. The body generates antigen-specific adaptive T cell anti-tumor immunity to eliminate malignancies in this proinflammatory milieu [154].

Dysbiosis is linked to poor response and toxicity to allogenic stem cell transplant treatment (allo-HSCT). Research that examined the feces of patients following HSCT discovered an excess of *Enterococcus, Streptococcus*, and different *Proteobacteria*, whereas *Faecalibacterium* and *Ruminococcus* were in low abundance. Furthermore, a low amount of 3-indoxyl sulfate was discovered in urine samples from individuals with worse survival after allo-HSCT. *Eubacterium limosum* enrichment was associated with a lower risk of recurrence

following HSCT, whereas a higher abundance of the genus *Blautia* was associated with increased overall survival [147].

10. Some methods used in therapeutic purpose

10.1. *Clostridium butyricum* and its metabolite butyrate

The *Clostridium* species is connected to infectious bacteria, as far as we know. We can observe this negative impact because some *Clostridium* species secrete exotoxins, such as the enterotoxin and alpha toxin from *Clostridium difficile* and *Clostridium perfingens,* respectively. On the other side, several species of Clostridium operate as probiotics and control the gut immune system [155].

Consider the *Clostridium* species as one of the primary bacterial communities in the human intestine. There are two significant clusters within it: *Clostridium* cluster IV, which includes *Clostridium leptum, Clostridium sporospaeroides, Clostridium cellulosi,* and *Faecalibacterium prausnitzii,* and *Clostridium* cluster XIVa, which has 21 species. One of the probiotics, *F. prausnitizii,* reduces inflammation by preventing NF-kB activation and IL8 production. To combat inflammation, these bacteria can also form biofilms and increase the TLR2-dependent release of IL-10 and IL-12 [155].

Clostridium species can use two metabolic pathways to create butyrate: one is the butyl-CoA transfuse, which is used by a variety of species, including *F. prausnitzii, Coprococcus eutactus,* and *Roseburia species*. The butyrate kinase pathway is the other pathway seen in *C.butyricum, Coproccus eutactus,* and *Coprococcus* comes. Through the actions of thiolas, 3-hydroxybutyrylCoAdehydrogenase, phosphotransbutyryllase, and butyrate kinase, Acetyl-CoA is converted into butyrate. Additionally, butyrate can be created through the breakdown of amino acids. The colonic epithelial cells' preferred energy source (butyrate) also has anti-inflammatory properties and lowers the mucosa's pH, reducing the solubility of bile salt and inhibiting ammonia absorption. Butyrate has been found to boost the colon's production of the hormone glucagon-like peptide-1 (GLP-1). The abundance of *Clostridium* clusters IV and XIVa rises in the presence of various fibers such as inulin oligofructose, arabinoxylan, guar gum, and resistant starch because *Clostridium* likes carbohydrates as food sources, particularly non-starch polysaccharides [155], [156].

One of the helpful bacteria in the gut is *C. butyricum*, which prevents antibiotic resistance, inhibits the gastrointestinal infection brought on by dysbiosis, and can grow specific good bacteria like *Lactobacillus* and *Bifidobacterium.* It is used as an over-the-counter probiotic in Japan, Korea, and China to treat diarrhea [37], [38].

The positive effects of *Clostridium butyricum* are caused by butyrate synthesis, which causes goblet cells to secrete more mucus. Additionally, *C. butyricum* increases tight junction protein expression, strengthening the mucosal barrier's ability to function. Additionally, *C. butyricum* increases the formation of anti-inflammatory lipids such as prostaglandin metabolites and palmitoleic acid [156].

Due to its capacity to enhance TGF- secretion, which promotes Treg differentiation, *C. butyricum* strain MIYAIRI 588 (CBM588) strengthens the immune response in the gut. It has been demonstrated that these bacteria cause colonic dendritic cells to express TGF-β is a Toll-like receptor 2 (TLR-2)-dependent manner. Additionally, due to increased Treg levels, *C. butyricum* plays a part in inhibiting Th1, Th2, and Th17-mediated inflammations. Through the stimulation of the Akt Pathway, *C. butyricum* protects neurons and prevents cell damage. A protein kinase with a serine/threonine specificity called Akt promotes cell viability and prevents apoptosis. As it promotes the expression of insulin receptor substrate 1 (IRS-1), which controls insulin signaling, the Akt pathway also contributes to glucose regulation. Therefore, because it inhibits insulin resistance brought on by IRS protein dysregulation, *C. butyricum* positively impacts diabetes. CMB588 strengthens the mucosal barrier function by increasing T cell overexpression in the colon lumina propria through IL-17A and plasma cells [156]–[158].

CBM588 noted that it worked well for treating childhood diarrhea. Vancomycin was administered in addition to CMB588; however, the co-administration of *Enterococcus faecium* did not have the same efficiency in treating *C. difficile* infection. According to studies, *C. butyricum* prevents botulism, an acute paralytic condition brought on by Botulinum neurotoxin (BoNt) and found in wounds of the intestine. Additionally, NEC, a devastating gastrointestinal disorder characterized by abdominal distension, gastrointestinal hemorrhage, and mucosal ulcers, is prevented by *C. butyricum*. It is interesting to note the association between antibiotic-associated diarrhea and some *C. butyrium* species, which harm the gut, like that of NEC, as well as the *C. butyricum* strain (NOR33234), has been observed [156]–[158].

There are many advantages to butyric acid. Because butyric acid has an anti-inflammatory impact by reducing the effect of NK-kB, one of these advantages is its protective effect against the side effects of several medications, such as aspirin and COX2 inhibitors. TNF-, IL-2, IL-6, IL-8, and IL-12 are inflammatory modulators whose expression is regulated

by NK-kb. Because of this, Mesalazine and sodium butyrate are used to treat inflammatory bowel disease. Because it boosts hemoglobin production, butyric acid is also used to treat sickle cell anemia. Additionally, because ornithine transcarbamylase deficiency affects these patients, butyric acid is utilized to treat patients with enzymatic urea cycle deficits. The biosynthesis of apolipoproteins and the manufacture of cholesterol can be affected by butyric acid. Butyric acid also has other use in vascular stroke and obesity [159]. As more than 300 mg of butyric acid are needed daily but cannot be pharmaceutically manufactured, the standard dose of 150–300 mg is regarded as 15–30 percent of the daily requirement dose [160].

10.2. The promising role of *Akkermansia muciniphila*

Akkermansia muciniphila is a gram-negative anaerobic, non-motile bacterium that degrades mucin in the intestine's mucus layer. They are the only *Verrucomicrobia* species found in the human stomach. *A.muciniphila* colonizes the gut within the first year of life but declines with time. These bacteria are also transmitted to the newborn through nursing since they are present in human milk and may break down the oligosaccharides in the infant's stomach [84], [161], [162]. *A. muciniphila* 's potential toxicity was mainly attributed to its attachment process to degrade the intestinal mucus layer. As mucin-degrading agent, they primarily stay in the outside mucosal layer and does not reach the inner mucosal layer. Pathogenic germs must get through the inner layer. Although *A. muciniphila* possesses LP, it is not implicated in endotoxemia [84].

The presence of oxygen affects the development of *A. muciniphila.* It was shown that they could withstand and even benefit from nanomolar quantities of oxygen in liquid media. Acetate to propionate synthesis by *A. muciniphila* changes in the presence of oxygen. Therefore, it causes an increase in the generation of ATP and NADH, which promotes the development of the bacteria [163].

As a mucin degradant, *Akkermansia muciniphila* plays a role in immunological control, such as regulating TNF-α, INF-γ, IL-4, and IL-10. Low levels of anti-inflammatory cytokines IL-10 and IL-4, as well as high levels of pro-inflammatory cytokines TNF- α and INF-γ, have been associated with a high abundance of *Akkermansia muciniphila* [84].

The mucosal layer of the gut protects epithelial cells against microbial assault. *A. muciniphila* deficiency in the gut promotes mucosal thinning, lowering intestinal barrier function and making it easier for toxins to enter the host. *A. muciniphila* also aids in energy

associated with glucose, protein, and lipid metabolism. *Akkermansia muciniphila* can control the host immune system and increase the integrity of intestinal epithelial cells and mucus layer thickness, promoting intestinal health [84],[163]–[165]. Furthermore, *Akkermansia muciniphila* can´t only degrade mucins but also stimulate mucin production [166]. *Akkermansia muciniphila* is also found in the oral cavity; however, its function is unclear. They are hypothesized to increase epithelial cell mucus production, protecting them against pathogen invasion [163].

It was discovered that consumption of *A. muciniphila* restored endogenous synthesis of antimicrobial peptides. In addition, *A. muciniphila* increased the endogenous production of specific bioactive lipids that belong to the endocannabinoid family, which have anti-inflammatory properties, as well as regulating the endogenous production of gut peptides involved in glucose regulation and gut barrier, glucagon-like peptide-1 and 2. (GLP-1 and GLP-2) [162].

Propionic acid, one of the bacteria´s metabolites, was also found in the mucus layer near the intestinal epithelial cells. Propionic acid can interact with Gpr43 (G protein-coupled receptor 43), whereas other short-chain fatty acids interact with Gpr41, resulting in a cascade of downstream pathway alterations to produce immunomodulatory effects [84], [161]. In addition, these bacteria produce other SCFAs, such as acetate and a small amount of 1,2-propanediol and succinate. Sugars degraded by *A. muciniphila* include glucose, N-Acetylglucosamine (GlcNAc), N-Acetylgalactosamine (GalNAc), and fucose [161], [163].

The strain type of *A. muciniphila* (MucT) was shown to be resistant to vancomycin, metronidazole, and penicillin but sensitive to imipenem, piperacillin/tazobactam, and doxycycline. Another strain of *A. muciniphila* was vancomycin and ofloxacin resistant but sensitive to penicillin, amoxicillin, ceftriaxone, and imipenem [163].

A low abundance of *Akkermansia muciniphila* was associated with some metabolic disorders and inflammatory diseases, such as obesity, T2D, IBD, and Autism. In contrast, a high abundance of these bacteria was linked with colorectal cancer [84], [161]–[164], [166]. *Akkermansia muciniphila* was reported to be high in association with the treatment with metformin in diabetic patients. *Akkermansia muciniphila* can improve the glucose and lipid metabolism [84], [161], [162], [165], [166]. *Akkermansia muciniphila* was also correlated to atopic diseases in children, as a low quantity of the bacteria has been reported in atopic children. It is suggested that *Akkermansia muciniphila* may enhance the epithelial cell to secret IL-8 for an immune response [84]. *A. muciniphila*-based sequences were decreased in children who had taken several antibiotic courses. Therefore, they were at risk for obesity later in life in a large

study of babies in daycare [163]. An energy-dense or nutritionally unbalanced diet, such as a high-fat diet, high fat-high sugar diet (HFHS), or high fat-high cholesterol diet (HFHC), may reduce the abundance of *A. muciniphila* in humans, which could be due to a change in the gut microenvironment caused by a surplus in gut nutrition. This unbalanced diet reduces *A. muciniphila* 's competitive advantage [161].

Polyphenols or polyphenol-rich foods such as cranberry, lingonberry, non-absorbable apple procyanidins, and grape polyphenols have been shown to dramatically ameliorate HF-induced problems, accompanied by an increase in the abundance of *Akkermansia muciniphila. Consumption* of fermented and unfermented herbal medications such as *Flos Lonicera*, *Rhizoma Atractylodis Macrocephalae*, and *Aguamiel* (rich in saponin) may also boost *A. muciniphila* abundance in the stomach. These diets and herbal medicine may be suggested to increase these bacteria to benefit from their advantages [161], [165], [166].

Amuc 1100, an outer membrane protein of *A. muciniphila* that may be beneficial. Amuc 1100 remained stable after pasteurization and interacted with Toll-like receptor 2 to increase intestinal barrier integrity. Amuc 1100 has the potential to activate TLR2 and TLR4 to boost IL-10 production, hence modulating immunological response and intestinal barrier function. This discovery is crucial because it suggests the use of *A. muciniphila* in clinical therapy [84], [161], [162], [164], [165].

Many studies have found that combining gut microbiota with anti-PD1 antibodies in cancer treatment is beneficial. A study discovered a beneficial effect of combining *Akkermansia muciniphila* as a probiotic with the immune checkpoint inhibitor PD-1 antibody [84], [165].

10.3. Probiotics, prebiotics, and synbiotics

For a long time, we employed prebiotics or probiotics in our nutrition goods, such as yoghurt or cheese, but we never acknowledged their connection to the Gut-brain axis. We consider the importance and application of probiotics, prebiotics, and synbiotics in the treatment of various diseases, such as their positive effect on irritable bowel syndrome, elimination of Helicobacter, inflammatory bowel diseases, or allergic diseases, until recent decades and intensive research on this bidirectional way of communication between the brain and the gut. Their usefulness has also been demonstrated in the treatment of obesity and diabetes. Furthermore, prebiotics and probiotics can help prevent several forms of cancer [14].

10.3.1. Probiotics

The commonly used probiotics are *Lactobacillus, Bifidobacterium, Streptococcus, Enterococcus* and *Lactococcus*. In addition, fungi strains can be used, such as *Saccharomyces* [14], [167], [168]. Probiotics may contain either a single strain or a combination of many strains, such as #VSL3, a mixture of eight strains [167].

Probiotics help to maintain the balance of harmful and helpful bacteria in the gut by regulating the growth of microbiota, which are essential for everyday activities. They can also restore the natural condition of gut microbiota following antibiotic therapy. Furthermore, probiotics inhibit the growth of harmful bacteria such as *Clostridium perfringens, Campylobacter jejuni, Salmonella enteritidis, Escherichia coli, Shigella, Staphylococcus,* and *Yersinia* species, hence avoiding food poisoning. Probiotics aid digestion and have a good impact on the treatment of food allergies, candidiasis, and dental cavities. Natural manufacturers of *B group vitamins (B1, B2, B3, B6, B8, B9, B12) are Bifidobacterium adolescentis and Bifidobacterium pseudocatenulatum.* They also boost the immune system's function, improve vitamin and mineral absorption, and promote organic and amino acid production. Probiotic microbes may also be capable of producing enzymes, such as esterase, lipase, and coenzymes A, Q, NAD, and NADP. Some probiotic metabolic products may have antibacterial (acidophiline, bacitracin, lactacin), anti-cancerogenic, and immunosuppressive effects. Furthermore, Probiotics stimulate immune function by increasing immunoglobulin levels, boosting macrophage and lymphocyte activities, and increasing γ-interferon synthesis [14], [167], [168]. Genetically engineered bacteria can produce molecules such as insulin, androgens, estrogens, growth hormone, or cholesterol-lowering compounds. One of the interest goals is the formation of medications or hormones in situ for lengthy periods that are continually required by persons suffering from various ailments, such as diabetic patients or hypercholesterolemia [168]. Probiotics' anti-tumor effect is thought to be mediated by the following mechanisms: 1) Modifying immunological activities related to immune response 2) Antiproliferative effects via apoptosis and cell differentiation control 3) Inhibiting the formation of enzymes such as β-glucuronidase, urease, choloylglycine hydrolase, azedoreductase, and nitro-reductase by pathogenic bacteria, particularly entero-pathogens such as *E. coli* and *Clostridium perfringens*. Pro-carcinogens are converted to proximate carcinogens by beta-glucosidase and urease. Through the production of SCFAs under culture conditions,

Propionibacterium freudenreichii was demonstrated to trigger cell death in human colon and stomach cancer cell lines [167], [168].

Some probiotics' effectiveness in preventing diarrhea is likely related to their capacity to protect the body from toxins. Suppressing metabolic events that produce toxins is also related to activating pathways with native enzymes, vitamins, and antimicrobial compounds. The administration of *Saccharomyces boulardii* yeast to individuals suffering from acute, watery diarrhea resulted in a cure and a reduction in the frequency. Probiotic strains have also effectively treated nosocomial, non-nosocomial, and viral diarrheas. It has been discovered that probiotics may boost the quantity of IgA antibodies, therefore halting a viral infection. Antibiotic-associated diarrhea (AAD) is a common side effect of antibiotics, as well as *Clostridium difficile* disease (CDD), which is also triggered by antibiotics and is a primary cause of nosocomial diarrhea and colitis epidemics. Probiotics of various varieties show promise as effective treatments for these two disorders. Three kinds of probiotics (*Saccharomyces boulardii, Lactobacillus rhamnosus GG,* and *probiotic combinations*) has been demonstrated to minimize the onset of antibiotic-associated diarrhea considerably. Only *S. boulardii* successfully treated CDD[14], [167]. Viable lactic acid bacteria (LAB) reduce and prevent diarrhea [168].

Some probiotics interact with drugs, such as warfarin, Vitamin K dependent, and bifolac. Bifolac, a probiotic, helps to restore the gut environment and treat gastrointestinal diseases. *Lactobacillus rhamnosus* and *Bifidobacterium longum* are two bacteria strains found in Bifolac. Furthermore, medications destroy gut flora, which might be probiotics. As a result, it is usually best to take probiotics at least two hours after taking antibiotics. *S. boulardii* can also interact with antifungal medications. Florastor, which contains *S. boulardii*, should not be used with oral antifungal drugs. Probiotics should also be taken with caution in patients on immunosuppressants such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic drugs because probiotics can induce infection or pathogenic colonization in immunocompromised people [169].

10.3.2. Prebiotics

Prebiotics are either natural products, such as fruits, vegetables, cereals and other herbal sources of carbohydrate, or synesthetic products, such as lactulose, galacto-oligosaccharides, fructo-oligosaccharides, malto-oligosaccharides, cyclodextrins, and lactosaccharose [14], [170].

Prebiotics can be used instead of probiotics. Prebiotics are superior to probiotics since they resist the effects of GIT acids, proteases, and bile salts. Prebiotics also improve the selectivity and proliferation of some microorganisms. Furthermore, prebiotics lower intestinal pH and sustain osmotic water retention in the intestine. Excess prebiotics, on the other hand, may cause gas and diarrhea. Prebiotics can be consumed indefinitely and for preventive purposes [14], [168], [170].

10.3.3. Synbiotics

Synbiotics are probiotics and prebiotics combined to enhance their benefits. The most common symbiotic is the combination of *Bifidobacterium* or *Lactobacillus* with fructo-oligosaccharides. The probiotics are primarily active in both the small and large intestines, and the action of a prebiotic is detected mainly in the large intestine. Thus, the combination of the two may have a synergistic effect [14], [167], [168], [170].

Synbiotics lower the quantities of unwanted metabolites while also inactivating nitrosamines and cancer-causing chemicals. Their usage increases the amounts of short-chain fatty acids, ketones, carbon disulphides, and methyl acetates, which may have a good influence on the host's health. Regarding medicinal effectiveness, synbiotics' desired qualities include antibacterial, anticancerogenic, and anti-allergic actions. They help reduce constipation and diarrhea by inhibiting degradation processes in the colon. Synbiotics are particularly effective in preventing osteoporosis, lowering blood fat and sugar levels, controlling the immune system, and treating brain diseases related to improper hepatic function [14], [167].

Lactobacilli, Bifidobacteria spp, *S. boulardii, B. coagulans,* and other probiotic strains are used in synbiotic formulations. In contrast, the major prebiotics used in synbiotics are oligosaccharides, such as fructo-oligosaccharide (FOS), GOS, and xylo-oligosaccharides (XOS), inulin, and those from natural sources such as chicory and yacon roots [167]. SYNCAN project has proved the efficacy of the symbiotic, which contains fructo-oligosaccharides (SYN1), *Lactobacillus rhamnosus* GG, and *Bifidobacterium animalis* subsp. *Lactis* Bb12 in patients with a high risk of developing colorectal cancer [14]. Preneoplastic lesions are inhibited by dietary delivery of *B. longum,* oligofructose, and inulin. Furthermore, *B. longum* inhibited mammary and colon cancer [167].

10.3.4. Postbiotics

Postbiotics are bacterial metabolites, such as bacteriocins, organic acids, ethanol, diacetyl, acetaldehydes, and hydrogen peroxide. They also contain certain heat-killed probiotics that can benefit biological activity in the gut. Postbiotics may inhibit the development of pathogenic bacteria; therefore, they are used alternative to antibiotics. The postbiotics are non-toxic, non-pathogenic and resist being inactivated by human enzymes [170].

10.4. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is the practice of transplanting fecal bacteria and their metabolites from healthy people to people with serious illnesses. FMT has been used to treat *Clostridium difficile* infections that are recurring or resistant (CDI). It's also used to treat metabolic syndrome, diabetes, Crohn's disease, Parkinson's disease, multiple sclerosis, psoriasis, irritable bowel syndrome, inflammatory bowel disorders, Autism, anorexia nervosa, and Alzheimer's disease. More research is needed to show its efficacy in clinical settings [13], [171]–[174]. FMT is not a novel therapy, but it has been utilized in the past; in China, many people were treated for food poisoning and diarrhea with "yellow soup," a mixture of fresh feces and water. Furthermore, during WWII, German soldiers in Northern Africa given camel dung to cure dysentery [172].

FMT has been approved by the United States food and drug administration (FDA) since 2013 to treat recurrent and refractory CDI. FMT is classified as a "New Biologic Drug" by Health Canada, and all clinical trials must go through the clinical trial application procedure to verify it fulfils quality and safety criteria. FMT is also licensed for the treatment of CDI in the United Kingdom, where it is considered safe and effective [13], [174].

To be successful, the FMT method must adhere to certain guidelines. To avoid illness transmission from donor to receiver, the donor must be completely healthy [13], [172], [173], [175]. Jiunn-Wei Wang et al. declared in their review article the inclusion and exclusion criteria for donors and the recommended investigations [13]. Proton pump inhibitors, aspirin, steroids, immunosuppressants, antibiotics, and antibiotics should not be used by donors [171]. Preparation is also required for the receiver, as he should not have taken any antibiotics in the past 12-48 hours before the treatment, and only colon cleansing procedures are performed using

enemas, laxatives, or broad-spectrum antibiotics. Most people use macrogol for intestinal lavage. Some studies recommend taking loperamide an hour before the procedure to guarantee that the fecal sample remains in the gut for at least four hours [13], [172], [173]. Some studies show that pretreatment with antibiotics prior to FMT is effective in people with ulcerative colitis. Antibiotic therapy following FMT increases the likelihood of process failure. Metformin, statins, antihypertensives, platelet inhibitors, antidepressants, and opiates all have a considerable impact on gut microbial makeup. In FMT, the donor's gender must also be considered [172], [173].

FMT was thought to be more successful when fecal material was obtained from the recipient's relatives. Still, recent research has shown that fecal material obtained from nonrelatives had the same efficacy as that obtained from close relative [171]. The FMT can be delivered to the patient via different ways, including oral through the upper stomach area or oral capsules, nasal, and rectal by colonoscopy or enema. Rectal colonoscopy is the optimum method for transferring because the transfer is deep in the cecum, lowering the likelihood of rapid fecal material evacuation. The transfer through nasogastric or nasoduodenal tube may result in difficulties owing to receiving a great abundance of germs in the upper digestive and respiratory tracts, which may induce pulmonary or gastrointestinal issues. An oral capsule is preferable to other routes of FMT delivery since it is less intrusive. Nonetheless, the large size of the capsule, as well as the danger of vomiting and aspiration, are regarded drawbacks [13], [171]–[173].

FMT has been demonstrated to be beneficial in a variety of conditions, including the treatment of recurrent D-lactic acidosis in a child with short bowel syndrome. FMT was also successful in individuals with refractory immune checkpoint inhibitor (ICI)-associated colitis [171]. According to a new study, FMT from an obese donor can accelerate weight gain, which focuses on the link between gut microbiota, obesity, and insulin resistance [172].

Bacteriophages influence the gene expression of their hosts and potentially decide their survival. Beneficial FMT effects might thus be mediated by the donor's phages altering the recipient's microorganisms. This idea becomes more plausible when you consider that most of the bacteria transferred during the FMT procedure may be dead, and it has been found that during the application of allogenic FMT in the metabolic syndrome, the sample from a healthy donor had a fecal phagosome, that was more like the donor than non-responders. This technique can potentially lower the risk of bacterial infections, but it does not usually prevent viral infections. Furthermore, large-scale human studies are required to demonstrate the viability of bacteriophage-based transplants in necessary conditions [172].

FMT is a biological medication that usually has adverse effects. Abdominal discomfort, constipation, gas, bloating, nausea, vomiting, diarrhea, blood in the stool, and fever are the most prevalent adverse effects. The use of endoscopy or colonoscopy to transfer the sample might result in physical harm or intestinal perforation [171].

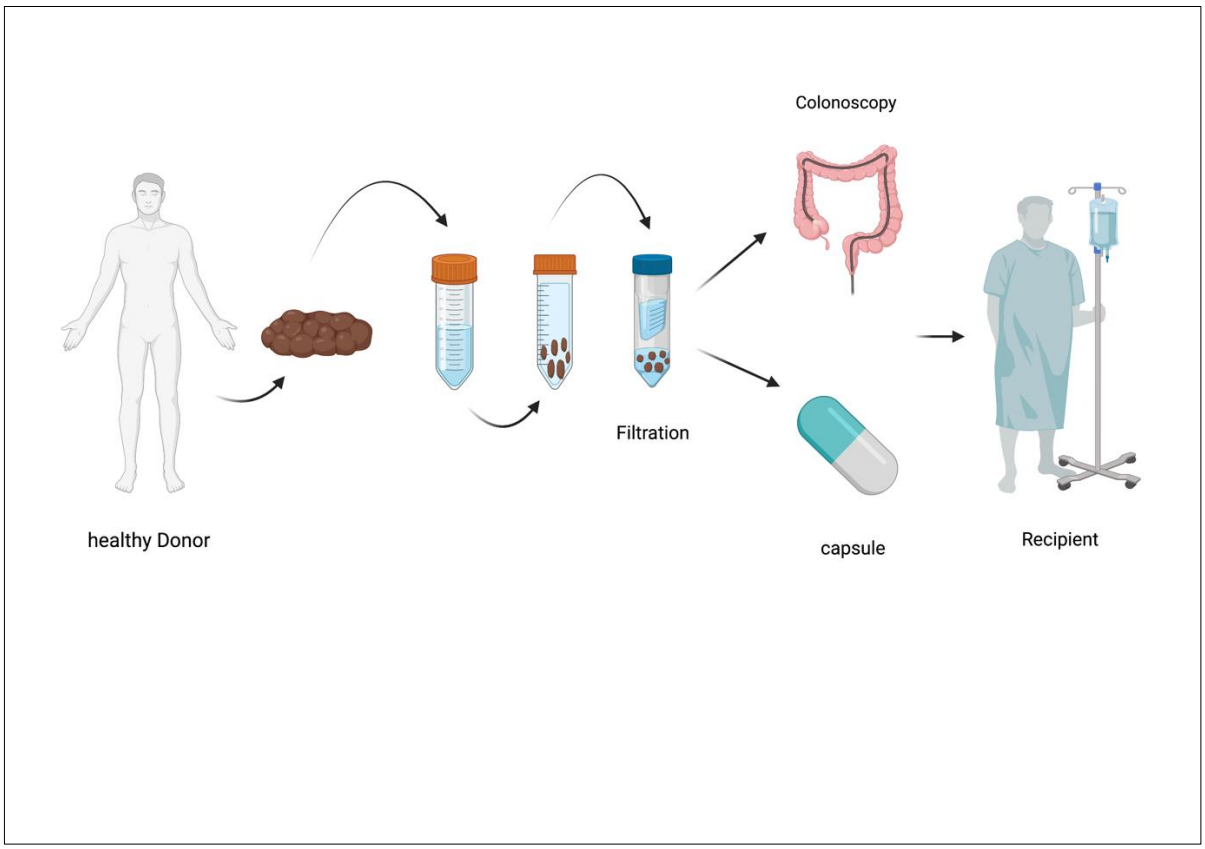

Figure 5. Schematic description of FMT process. As a fecal sample is acquired from a healthy donor who met the FMT requirements, it is combined with water and filtered. The sample will be delivered to the patient by numerous routes, one of which is colonoscopy or capsule [13].

11. Discussion

The bidirectional communication in the Gut-Brain axis has demonstrated its importance and role in various physiological functions, such as its effect on the intestinal immune system and neurotransmitter production, as well as various disorders, either neuropsychiatric or chronic, such as diabetes and cardiovascular diseases. SCFAs, such as acetic, butyric, and propionic acid, play an essential role in intestinal homeostasis and nervous system function [1],

[2]. Man acquires the gut microbiota throughout his life, beginning with the baby's birth and the infant's interaction with vaginal microbes. As a result, the delivery technique impacts health and may contribute to illnesses such as Asthma, Autism, and ADHD. C-section birth results in fewer complex microbiomes in the stomach. Breastfeeding also gives nutrients, probiotics, and antibiotics to the infant. Thus, breastfeeding is preferable to artificial feeding for the growth of beneficial gut bacteria [19]. Some illnesses affect males and females differently, such as depression, which affects ladies more than males. After examining the abundance of gut bacteria, was shown that depressed female patients had a higher concentration of *Actinobacteria* than healthy females. Furthermore, the gut microbiota can control the action of hormones and steroids, such as *Streptococcus* and *Bacillus* dysbiosis, which can create 5-reductase, which affects testosterone considerably. More research is needed to determine the gender variation in microbial status in the gut [21], [22].

The imbalance of gut microbiota and dysbiosis cause changes in human health and the emergence of numerous illnesses. Oral microbiotas have an important part in the etiology of schizophrenia, autism, rheumatoid arthritis, and type 2 diabetes [6], [39], [61], [93]. Man recognizes an important function of the Gut-brain axis in the etiology of neuropsychiatric illnesses. In Alzheimer's disease, LPS, a component of gram-negative bacteria's outer membrane, binds to TLR on the surface of microglia, triggering β-amyloid fibrillogenesis and boosting the inflammatory response [24]. Exotoxin generated by dysbiosis in chronic inflammation during Alzheimer's disease increases intestinal permeability, allowing pro-inflammatory cytokines to enter the systemic circulation and cross the BBB, activating microglia and astrocytes in the brain. The receptor of the advanced glycation end-product (RAGE), which is activated by amyloid protein and LPS9, is another component in chronic inflammation [3], [27]. The inflammatory response to misfolded α-synuclein activating microglial cells in the SNc, neural cells, and oligodendrocytes in Parkinson's disease generates oxidative stress, which interacts with microbial TLR2, resulting in an increase in TNF and IL-1 production as well as TLR expression. As a result, dopaminergic neurons in the SNc die [30]. Furthermore, Conventional Parkinson's disease (PD) treatments, notably catechol-o-methyltransferase (COMT) inhibitors and anticholinergics disturb the gut microbiota [33]. Schizophrenic patients have low BDNF levels. Greater BDNF levels are related to higher *Lactobacilli* and *Actinobacteria* levels and lower *Proteobacteria* and *Bacteriodetes* levels [31]. In depression, Indoleamine-2,3, dioxygenase (IDO) and tryptophan-2,3, -dioxygenase (TDO) enzymes convert tryptophan to serotonin. The activity of both enzymes is modulated by some gut microbiota, such as *B.infantis*, which has anti-depressive properties [42]. Antibiotics can

modify emotions in the human body. Both ceftriaxone and minocycline are antidepressants [43]. In ADHD patients, a high concentration of cyclohexadienyl dehydratase (CDT) enzyme has been linked to a high abundance of *Bifidobacterium*. CDT is an essential enzyme in synthesizing phenylalanine, a precursor to dopamine and noradrenaline. *Bacteroides* spp. were found to have a positive relationship with hyperactivity and impulsivity [11]. SCFAs disrupt the balance of excitation and inhibition, which substantially impacts epilepsy [66]. Additionally, Immune hyperactivity in autoimmune illnesses is connected to the role of gut bacteria in intestinal immune system maintenance. This connection aids in our understanding of the development of various autoimmune disorders, such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis. It may also provide light on the riddle of irritable bowel syndrome. It's worth noting that fungal infection worsens Crohn's disease while improving ulcerative colitis. *Malassezia restricta* is present not only on the skin but also in the intestinal mucosa of Crohn's disease patients [76]. The involvement of *Akkermansia* in MS is intriguing, as enrichment of these bacteria has been seen in MS patients with mild severity, indicating a positive impact. As a result, additional research is needed to determine how we might profit from their advantages [84]. TMAO, a serious bacterial metabolite, plays a crucial role in the pathogenesis of most common diseases, such as cardiovascular diseases, stroke, and diabetes. TMAO induces platelet aggregations, even in the presence of low-dose Aspirin [107]. As a result, the TMAO inhibitor is a prospective treatment for lowering the risk of cardiovascular disease and stroke. Branched-chain amino acids are another type of bacterial metabolite that increases the risk of T2D. In patients with insulin resistance, a high abundance of *Prevotellacopri* and *Bacteroides vulgatus* is related to a high level of BBCA [120]. Interesting in T1D is the role of GABA in activating β-cells and increasing insulin synthesis [123]. The enrichment of *A.muciniphila* after the treatment of metformin can explain the long action of metformin and its effectiveness; however, its short half-time [123], [130]. The “hygiene hypothesis” is suggested to explain the relationship between allergy and microbes. Lung microbiotas with gut microbiotas influence the pathogenesis of asthma [132]. The patients in Covid 19 had Gastrointestinal dysregulation, such as diarrhea, indicating the function of microbiotas. Furthermore, the gut microbiotas aid in the immune response to this virus and can suppress the production of ACE2 receptors. SARS-Cov2 enters the cell through ACE2. More research is needed to identify the beneficial bacteria in Covid 19 and the precise genome responsible for the ACE2 down-regulation [141]. Some dysbiosis cause cancer, such as *H. pylori* increase the risk of gastric cancer. Through its Fap2 protein, *F. nucleatum* may promote intestinal tumorigenesis by sticking to cancer cells and regulating immune cells [150],

[153]. Additionally, gut microbiotas influence the efficacy of anti-PD1 and CTLA-4 antibody drugs by improving the activity of the dendritic cells [146].

Exploiting the Gut-Brain axis´s advantage is widely applicable nowadays, but we need much research to develop many methods for treating various disorders. The use of bacteriophage to deliver the gut bacteria´s enzymes and metabolites is better than probiotics because of the possibility of these bacteria´s death or mutation. FMT process needs more research on humans, thus proving its effectiveness [13]. The advantages of butyric acid, an SFA, are various but hinder manufacturing pharmaceutically to provide the needed dose [159]. In contrast, the negative effect of propionic acid, another SFA, is anticipated, necessitating more investigation into these metabolites. Finally, the relevance of the Gut-brain axis in physiological processes and diseases cannot be overstated. Despite several studies in this sector, further research on humans is required to identify the other circumstances of gut bacteria.

Abbreviations:

2-AG	2-acylglycerol
2-OG	2-oleoylglycerol
2-PG	2-palmitoylglycerol
5-HT	Serotonin
AAD	Antibiotic-associated diarrhea
ACE2	Angiotensin-Converting Enzyme II
ACPAs	Anti-citrullinated protein antibodies
ACTH	Adrenocorticotrophic hormone
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
AGEs	advanced glycation end products
AhR	Aryl hydrocarbon receptor
AMPK	Adenosine monophosphate-activated protein kinase
Anti-CCP	Anticyclic citrullinated peptide
APCs	Antigen-presenting cells
ASD	Autism spectrum disorder
ATP	Adenosine triphosphate
BAs	Bile acids
BBB	Blood-brain barrier
BBCA	branched-chain amino acids
BDNF	Brain-derived neurotrophic factor
BoNt	Botulinum neurotoxin
CBR	Cannabinoid receptor
CC	Clara cell protein
CCD	*Clostridium difficile* disease
CCK	Cholecystokinin
CD	Coeliac disease
CD	Crohn's disease
CDI	*Clostridium difficile* infections
CDT	Cyclohexadienyl dehydratase
CLDN	Claudins
CNS	Centre nervous system

CNV	Copy numbers variation
COMT	Catechol-o-methyltransferase
COX2	Cytochrome C oxidase subunit 2
CpG-ON	CpG oligonucleotides
CRC	Colorectal cancer
CRF	Corticotrophin Releasing Factor
CRH	Cortisol-releasing hormone
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTLA-4	cytotoxic T-lymphocyte-associated Protein 4
CVD	Cardiovascular diseases
CXCL 16	Chemokine ligand 16
DA	Dopamine
DCs	Dendritic cells
DHNA	1,4-dihydroxy-2-naphthoic acid
DPP	Dipeptide Peptidase
ECS	Endocannabinoid system
ENS	enteric nervous system
EPO	Erythropoietin
ERK	extracellular signal-regulated kinase
FA	Fatty acid
FFAR	free fatty acid receptors
Fgf15	Fibroblast growth factor 15
FLS	Fibroblast-like synoviocytes
FMO	Flavin Monooxygenase
FMT	Fecal microbiome transport
FN	Febrile neutropenia
FODMAPs	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols,
FOS	Fructo- oligosaccharides
FXR	Farnesoid-X-receptor
G-CSF	Granulocyte-colony stimulating factor
GA	γ-amyloid
GABA	γ-aminobutyric acid
GAD	Glutamate decarboxylase

GalNAc	N-Acetylgalactosamine
GALT	Gut-associated lymphatic tissue
GBB	γ -butyrobetaine
GBF	germinated barley food
GC	Glucocorticoids
GI	Gastrointestinal tract
GIP	Glucose-dependent insulinotropic polypeptide
GlcNAc	N-Acetylglucosamine
GLP	Peptide-like glucagon
Glu	Glutamate receptors
GLUT	Glucose transporter
GLUT1 DS	Glucose Transporter 1 Deficiency Syndrome
GOS	Galacto-oligosaccharides
GPR	G-protein-coupled receptors
GR	Glucocorticoid receptors
H1N1	Influenza-A-Virus H1N1
H2S	Hydrogen sulfide
HbA_{1c}	glycated hemoglobin
HDAC	Histone deacetylase
HDL	high-density lipoprotein
HFD	high-fat diet
HFHC	high fat-high cholesterol diet
HFHS	high fat-high sugar diet
HLA	Human leukocyte antigen
HPA	Hypothalamic-pituitary-adrenal
HSCT	Human stem cell transplant
HUVEC	Human umbilical vein endothelial cell
iBALT	inducible bronchus-associated lymphoid tissue
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICI	Immune checkpoint inhibitor
IDO	Indoleamine-2,3, -dioxygenase
IECs	Intestinal epithelial
IgG	Immunoglobulin G

iGluRs	ligand-gated ionotropic glutamate receptors
IL	Interleukin
ILCs	Innate lymphoid cells
iNKT	invariant neutral kill T cells
IPA	3-indole propionic acid
iPSCs	induced pluripotent stem cells
IR	Insulin resistance
IRS2	Insulin receptor substrate 2
KD	ketogenic diet
KYNA	Kynurenic acid
LAB	lactic acid bacteria
LADA	latent autoimmune diabetes
LPS	Lipopolysaccharides
LTA	Lipoteichoic acid
Ltx A	Leukotoxin-A
LXR	Liver X receptors
MAA	Malondialdehyde-acetaldehyde adducts
MAIT	Mucosa-associated invariant T
MCP-1	Monocyte chemoattractant protein 1
MIA	maternal immune activation
MLN	mesenteric lymph nodes
mLNs	Mesentery of the small intestine and colon
MMP	Matrix metalloproteinase
MS	Multiple Sclerosis
NBRs	Nucleotide-binding receptors
NCD	noncommunicable disease
NE	Noradrenalin
NETs	Neutrophil extracellular traps
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFTs	Neurofibrillary tangles
NK	Natural Killer
NLRs	NOD-like receptors
NMDA	N-methyl-d-aspartate
NO	Nitric oxide

NSCLC	non-small cell lung cancer
NTFs	Neurotrophic factors
OMVs	outer membrane vesicles
OS	Overall survival
PAD	peptidyl arginine deiminases
PAG	Phenylacetylglutamine
PAMPs	Pathogen-associated molecular patterns
PCS	p-cresyl sulfate
PD	Parkinson's disease
PD-1	Programmed death-1
PFS	Progression-free survival
PGC-1	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol-3-kinase
PLN	pancreatic lymph node
PLP	Pyridoxal phosphate
PS	Phenyl sulfate
PSA	Purified capsular polysaccharide A
PTGER4	Prostaglandin E receptor 4
PTM	Posttranslational modification
PUFAs	Polyunsaturated fatty acids
PYY	Gut hormone peptide YY
QUIN	Quinolinic acid
RA	Rheumatoid arthritis
RAGE	Receptor for advanced glycation end-products
RAS	Renin-angiotensin system
RCC	Renal cell carcinoma
RCT	randomized controlled study
RF	Rheumatoid factor
RR-MS	relapsing-remitting multiple sclerosis
RSV	Respiratory syncytial virus
SAA	serum amyloid A
SARS-Cov-2	severe acute respiratory syndrome coronavirus 2
SBI	serum-derived bovine immunoglobulin

SCFAs	Short-chain fatty acids
SERT	Serotonin selective reuptake transporter
SGLT	Sodium-glucose cotransporter
SIBO	Small intestine bacterial overgrowth
SNP	single nucleotide polymorphism
SNs	Substantia nigra pars compacta
SSRIs	selective serotonin reuptake inhibitors
STAMP	specific targeted antimicrobial peptide
T1D	Diabetes type 1
T2D	Diabetes type 2
TDO	Tryptophan-2,3, -dioxygenase
TGF-β	Transforming growth factor beta
TGOS	Trans galactic oligosaccharides
TGR5	G-protein-coupled bile acid receptor 1
Th17	T helper 17
Tjp-1	Tight junction protein-1
TLR	Toll-like receptor
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TMRPSS2	Transmembrane protease serine 2
TNF	Tumour necrose factor
Treg	Regulatory T cells
TSLP	Thymic stromal production lymphopoietin
UC	Ulcerative colitis
VEGF	Vascular endothelial growth factor

References

[1] S. H. Rhee, C. Pothoulakis, and E. A. Mayer, “Principles and clinical implications of the brain-gut-enteric microbiota axis,” *Nature Reviews Gastroenterology and Hepatology*, vol. 6, no. 5. pp. 306–314, 2009. doi: 10.1038/nrgastro.2009.35.

[2] N. Gasaly, P. de Vos, and M. A. Hermoso, “Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation,” *Frontiers in Immunology*, vol. 12. Frontiers Media S.A., May 26, 2021. doi: 10.3389/fimmu.2021.658354.

[3] M. H. Janeiro, M. J. Ramírez, and M. Solas, “Dysbiosis and Alzheimer’s Disease: Cause or Treatment Opportunity?,” *Cellular and Molecular Neurobiology*, vol. 42, no. 2. Springer, pp. 377–387, Mar. 01, 2022. doi: 10.1007/s10571-020-01024-9.

[4] P. P. Chong, V. K. Chin, C. Y. Looi, W. F. Wong, P. Madhavan, and V. C. Yong, “The microbiome and irritable bowel syndrome - A review on the pathophysiology, current research and future therapy,” *Frontiers in Microbiology*, vol. 10, no. JUN. Frontiers Media S.A., 2019. doi: 10.3389/fmicb.2019.01136.

[5] M. Jin, Z. Qian, J. Yin, W. Xu, and X. Zhou, “The role of intestinal microbiota in cardiovascular disease,” *Journal of Cellular and Molecular Medicine*, vol. 23, no. 4. Blackwell Publishing Inc., pp. 2343–2350, Apr. 01, 2019. doi: 10.1111/jcmm.14195.

[6] W.-Z. Li, K. Stirling, J.-J. Yang, and L. Zhang, “Gut microbiota and diabetes: From correlation to causality and mechanism,” *World J Diabetes*, vol. 11, no. 7, pp. 293–308, Jul. 2020, doi: 10.4239/wjd.v11.i7.293.

[7] H. Zhou *et al.*, “Gut microbiota: A potential target for cancer interventions,” *Cancer Management and Research*, vol. 13. Dove Medical Press Ltd, pp. 8281–8296, 2021. doi: 10.2147/CMAR.S328249.

[8] M. Koszewicz *et al.*, “Dysbiosis is one of the risk factor for stroke and cognitive impairment and potential target for treatment,” *Pharmacological Research*, vol. 164. Academic Press, Feb. 01, 2021. doi: 10.1016/j.phrs.2020.105277.

[9] D. Noto and S. Miyake, “Gut dysbiosis and multiple sclerosis,” *Clinical Immunology*, vol. 235. Academic Press Inc., Feb. 01, 2022. doi: 10.1016/j.clim.2020.108380.

[10] P. Srikantha and M. Hasan Mohajeri, “The possible role of the microbiota-gut-brain-axis in autism spectrum disorder,” *Int J Mol Sci*, vol. 20, no. 9, May 2019, doi: 10.3390/ijms20092115.

[11] A. Checa-Ros, A. Jeréz-Calero, A. Molina-Carballo, C. Campoy, and A. Muñoz-Hoyos, “Current evidence on the role of the gut microbiome in ADHD pathophysiology and therapeutic implications,” *Nutrients*, vol. 13, no. 1. MDPI AG, pp. 1–32, Jan. 01, 2021. doi: 10.3390/nu13010249.

[12] S. Villapol, “Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome,” *Translational Research*, vol. 226. Mosby Inc., pp. 57–69, Dec. 01, 2020. doi: 10.1016/j.trsl.2020.08.004.

[13] J. W. Wang *et al.*, “Fecal microbiota transplantation: Review and update,” *Journal of the Formosan Medical Association*, vol. 118. Elsevier B.V., pp. S23–S31, Mar. 01, 2019. doi: 10.1016/j.jfma.2018.08.011.

[14] P. Markowiak and K. Ślizewska, “Effects of probiotics, prebiotics, and synbiotics on human health,” *Nutrients*, vol. 9, no. 9. MDPI AG, Sep. 15, 2017. doi: 10.3390/nu9091021.

[15] M. Grochowska, M. Wojnar, and M. Radkowski, “The gut microbiota in neuropsychiatric disorders,” *Acta Neurobiol Exp (Wars)*, vol. 78, no. 2, pp. 69–81, 2018, doi: 10.21307/ane-2018-008.
[16] M. Lyte, “Host-microbiota neuroendocrine interactions influencing brain and behavior,” *Gut Microbes*, vol. 5, no. 3, pp. 381–389, Apr. 2014, doi: 10.4161/gmic.28682.
[17] A. Farzi, E. E. Fröhlich, and P. Holzer, “Gut Microbiota and the Neuroendocrine System,” *Neurotherapeutics*, vol. 15, no. 1. Springer New York LLC, pp. 5–22, Jan. 01, 2018. doi: 10.1007/s13311-017-0600-5.
[18] M. Sochocka, K. Donskow-Łysoniewska, B. S. Diniz, D. Kurpas, E. Brzozowska, and J. Leszek, “The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer’s Disease—a Critical Review,” *Molecular Neurobiology*, vol. 56, no. 3. Humana Press Inc., pp. 1841–1851, Mar. 01, 2019. doi: 10.1007/s12035-018-1188-4.
[19] C. Milani *et al.*, “The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota,” 2017, doi: 10.1128/MMBR.
[20] M. Jaggar, K. Rea, S. Spichak, T. G. Dinan, and J. F. Cryan, “You’ve got male: Sex and the microbiota-gut-brain axis across the lifespan,” *Frontiers in Neuroendocrinology*, vol. 56. Academic Press Inc., Jan. 01, 2020. doi: 10.1016/j.yfrne.2019.100815.
[21] C. Holingue, A. C. Budavari, K. M. Rodriguez, C. R. Zisman, G. Windheim, and M. D. Fallin, “Sex Differences in the Gut-Brain Axis: Implications for Mental Health,” *Current Psychiatry Reports*, vol. 22, no. 12. Springer, Dec. 01, 2020. doi: 10.1007/s11920-020-01202-y.
[22] M. C. Audet, “Stress-induced disturbances along the gut microbiota-immune-brain axis and implications for mental health: Does sex matter?,” *Frontiers in Neuroendocrinology*, vol. 54. Academic Press Inc., Jul. 01, 2019. doi: 10.1016/j.yfrne.2019.100772.
[23] J. W. Kinney, S. M. Bemiller, A. S. Murtishaw, A. M. Leisgang, A. M. Salazar, and B. T. Lamb, “Inflammation as a central mechanism in Alzheimer’s disease,” *Alzheimer’s and Dementia: Translational Research and Clinical Interventions*, vol. 4. Elsevier Inc, pp. 575–590, Jan. 01, 2018. doi: 10.1016/j.trci.2018.06.014.
[24] P. Kesika, N. Suganthy, B. S. Sivamaruthi, and C. Chaiyasut, “Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer’s disease,” *Life Sciences*, vol. 264. Elsevier Inc., Jan. 01, 2021. doi: 10.1016/j.lfs.2020.118627.
[25] S. Wu, X. Liu, R. Jiang, X. Yan, and Z. Ling, “Roles and Mechanisms of Gut Microbiota in Patients With Alzheimer’s Disease,” *Frontiers in Aging Neuroscience*, vol. 13. Frontiers Media S.A., May 28, 2021. doi: 10.3389/fnagi.2021.650047.
[26] M. Sochocka, K. Donskow-Łysoniewska, B. S. Diniz, D. Kurpas, E. Brzozowska, and J. Leszek, “The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer’s Disease—a Critical Review,” *Molecular Neurobiology*, vol. 56, no. 3. Humana Press Inc., pp. 1841–1851, Mar. 01, 2019. doi: 10.1007/s12035-018-1188-4.
[27] C. Jiang, G. Li, P. Huang, Z. Liu, and B. Zhao, “The Gut Microbiota and Alzheimer’s Disease,” *Journal of Alzheimer’s Disease*, vol. 58, no. 1. IOS Press, pp. 1–15, 2017. doi: 10.3233/JAD-161141.
[28] F. Angelucci, K. Cechova, J. Amlerova, and J. Hort, “Antibiotics, gut microbiota, and Alzheimer’s disease,” *J Neuroinflammation*, vol. 16, no. 1, May 2019, doi: 10.1186/s12974-019-1494-4.

[29] K. Kowalski and A. Mulak, “Brain-gut-microbiota axis in Alzheimer’s disease,” *J Neurogastroenterol Motil*, vol. 25, no. 1, pp. 48–60, Jan. 2019, doi: 10.5056/jnm18087.

[30] V. Caputi and M. C. Giron, “Microbiome-gut-brain axis and toll-like receptors in parkinson’s disease,” *International Journal of Molecular Sciences*, vol. 19, no. 6. MDPI AG, Jun. 06, 2018. doi: 10.3390/ijms19061689.

[31] M. F. Sun and Y. Q. Shen, “Dysbiosis of gut microbiota and microbial metabolites in Parkinson’s Disease,” *Ageing Research Reviews*, vol. 45. Elsevier Ireland Ltd, pp. 53–61, Aug. 01, 2018. doi: 10.1016/j.arr.2018.04.004.

[32] M. Lubomski, A. H. Tan, S. Y. Lim, A. J. Holmes, R. L. Davis, and C. M. Sue, “Parkinson’s disease and the gastrointestinal microbiome,” *Journal of Neurology*, vol. 267, no. 9. Springer, pp. 2507–2523, Sep. 01, 2020. doi: 10.1007/s00415-019-09320-1.

[33] F. Lv *et al.*, “The role of microbiota in the pathogenesis of schizophrenia and major depressive disorder and the possibility of targeting microbiota as a treatment option,” 2017. [Online]. Available: www.impactjournals.com/oncotarget/

[34] B. Golofast and K. Vales, “The connection between microbiome and schizophrenia,” *Neuroscience and Biobehavioral Reviews*, vol. 108. Elsevier Ltd, pp. 712–731, Jan. 01, 2020. doi: 10.1016/j.neubiorev.2019.12.011.

[35] K. W. Hoffman, J. J. Lee, C. M. Corcoran, D. Kimhy, T. M. Kranz, and D. Malaspina, “Considering the Microbiome in Stress-Related and Neurodevelopmental Trajectories to Schizophrenia,” *Frontiers in Psychiatry*, vol. 11. Frontiers Media S.A., Jul. 03, 2020. doi: 10.3389/fpsyt.2020.00629.

[36] N. Munawar *et al.*, “Hidden role of gut microbiome dysbiosis in schizophrenia: Antipsychotics or psychobiotics as therapeutics?,” *International Journal of Molecular Sciences*, vol. 22, no. 14. MDPI, Jul. 02, 2021. doi: 10.3390/ijms22147671.

[37] T. Halverson and K. Alagiakrishnan, “Gut microbes in neurocognitive and mental health disorders,” *Annals of Medicine*, vol. 52, no. 8. Taylor and Francis Ltd., pp. 423–443, Nov. 16, 2020. doi: 10.1080/07853890.2020.1808239.

[38] S. Martin, A. Foulon, W. el Hage, D. Dufour-Rainfray, and F. Denis, “Is There a Link between Oropharyngeal Microbiome and Schizophrenia? A Narrative Review,” *International Journal of Molecular Sciences*, vol. 23, no. 2. MDPI, Jan. 01, 2022. doi: 10.3390/ijms23020846.

[39] F. Dickerson, E. Severance, and R. Yolken, “The microbiome, immunity, and schizophrenia and bipolar disorder,” *Brain Behav Immun*, vol. 62, pp. 46–52, May 2017, doi: 10.1016/j.bbi.2016.12.010.

[40] M. v. Seeman, “The gut microbiome and antipsychotic treatment response,” *Behavioural Brain Research*, vol. 396, Jan. 2021, doi: 10.1016/j.bbr.2020.112886.

[41] T. Szeligowski, A. L. Yun, B. R. Lennox, and P. W. J. Burnet, “The Gut Microbiome and Schizophrenia: The Current State of the Field and Clinical Applications,” *Frontiers in Psychiatry*, vol. 11. Frontiers Media S.A., Mar. 12, 2020. doi: 10.3389/fpsyt.2020.00156.

[42] A. S. Carlessi, L. A. Borba, A. I. Zugno, J. Quevedo, and G. Z. Réus, “Gut microbiota–brain axis in depression: The role of neuroinflammation,” *European Journal of Neuroscience*, vol. 53, no. 1. Blackwell Publishing Ltd, pp. 222–235, Jan. 01, 2021. doi: 10.1111/ejn.14631.

[43] S. Liang, X. Wu, X. Hu, T. Wang, and F. Jin, “Recognizing depression from the microbiota–gut–brain axis,” *International Journal of Molecular Sciences*, vol. 19, no. 6. MDPI AG, Jun. 01, 2018. doi: 10.3390/ijms19061592.

[44] Y. Du, X. R. Gao, L. Peng, and J. F. Ge, “Crosstalk between the microbiota-gut-brain axis and depression,” *Heliyon*, vol. 6, no. 6. Elsevier Ltd, Jun. 01, 2020. doi: 10.1016/j.heliyon.2020.e04097.

[45] F. Huang and X. Wu, “Brain Neurotransmitter Modulation by Gut Microbiota in Anxiety and Depression,” *Frontiers in Cell and Developmental Biology*, vol. 9. Frontiers Media S.A., Mar. 11, 2021. doi: 10.3389/fcell.2021.649103.

[46] G. Winter, R. A. Hart, R. P. G. Charlesworth, and C. F. Sharpley, “Gut microbiome and depression: What we know and what we need to know,” *Reviews in the Neurosciences*, vol. 29, no. 6. Walter de Gruyter GmbH, pp. 629–643, Aug. 28, 2018. doi: 10.1515/revneuro-2017-0072.

[47] A. K. Capuco Ivan Urits Jamal Hasoon Rebecca Chun Brittany Gerald Jason Wang Hisham Kassem Anh L Ngo Alaa Abd-Elsayed Thomas Simopoulos Alan D Kaye Omar Viswanath *et al.*, “Current Perspectives on Gut Microbiome Dysbiosis and Depression,” *Adv Ther*, vol. 37, doi: 10.6084/m9.figshare.11865615.

[48] J. Schachter *et al.*, “Effects of obesity on depression: A role for inflammation and the gut microbiota,” *Brain, Behavior, and Immunity*, vol. 69. Academic Press Inc., pp. 1–8, Mar. 01, 2018. doi: 10.1016/j.bbi.2017.08.026.

[49] W. Z. Hao, X. J. Li, P. W. Zhang, and J. X. Chen, “A review of antibiotics, depression, and the gut microbiome,” *Psychiatry Research*, vol. 284. Elsevier Ireland Ltd, Feb. 01, 2020. doi: 10.1016/j.psychres.2019.112691.

[50] J. M. Peirce and K. Alviña, “The role of inflammation and the gut microbiome in depression and anxiety,” *Journal of Neuroscience Research*, vol. 97, no. 10. John Wiley and Sons Inc, pp. 1223–1241, Oct. 01, 2019. doi: 10.1002/jnr.24476.

[51] C. A. Simpson, C. Diaz-Arteche, D. Eliby, O. S. Schwartz, J. G. Simmons, and C. S. M. Cowan, “The gut microbiota in anxiety and depression – A systematic review,” *Clinical Psychology Review*, vol. 83. Elsevier Inc., Feb. 01, 2021. doi: 10.1016/j.cpr.2020.101943.

[52] G. Fowlie, N. Cohen, and X. Ming, “The perturbance of microbiome and gut-brain axis in autism spectrum disorders,” *International Journal of Molecular Sciences*, vol. 19, no. 8. MDPI AG, Aug. 01, 2018. doi: 10.3390/ijms19082251.

[53] E. Garcia-Gutierrez, A. Narbad, and J. M. Rodríguez, “Autism Spectrum Disorder Associated With Gut Microbiota at Immune, Metabolomic, and Neuroactive Level,” *Frontiers in Neuroscience*, vol. 14. Frontiers Media S.A., Oct. 08, 2020. doi: 10.3389/fnins.2020.578666.

[54] J. G. Mulle, W. G. Sharp, and J. F. Cubells, “The gut microbiome: A new frontier in autism research,” *Curr Psychiatry Rep*, vol. 15, no. 2, Feb. 2013, doi: 10.1007/s11920-012-0337-0.

[55] H. E. Vuong and E. Y. Hsiao, “Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder,” *Biological Psychiatry*, vol. 81, no. 5. Elsevier USA, pp. 411–423, Mar. 01, 2017. doi: 10.1016/j.biopsych.2016.08.024.

[56] Y. Yang, J. Tian, and B. Yang, “Targeting gut microbiome: A novel and potential therapy for autism,” *Life Sciences*, vol. 194. Elsevier Inc., pp. 111–119, Feb. 01, 2018. doi: 10.1016/j.lfs.2017.12.027.

[57] H. K. Hughes, D. Rose, and P. Ashwood, “The Gut Microbiota and Dysbiosis in Autism Spectrum Disorders,” *Current Neurology and Neuroscience Reports*, vol. 18, no. 11. Current Medicine Group LLC 1, Nov. 01, 2018. doi: 10.1007/s11910-018-0887-6.

[58] V. Saurman, K. G. Margolis, and R. A. Luna, “Autism Spectrum Disorder as a Brain-Gut-Microbiome Axis Disorder,” *Digestive Diseases and Sciences*, vol. 65, no. 3. Springer, pp. 818–828, Mar. 01, 2020. doi: 10.1007/s10620-020-06133-5.

[59] M. V. Ristori *et al.*, “Autism, gastrointestinal symptoms and modulation of gut microbiota by nutritional interventions,” *Nutrients*, vol. 11, no. 11. MDPI AG, Nov. 01, 2019. doi: 10.3390/nu11112812.

[60] J. Pulikkan, A. Mazumder, and T. Grace, “Role of the Gut Microbiome in Autism Spectrum Disorders,” in *Advances in Experimental Medicine and Biology*, vol. 1118, Springer New York LLC, 2019, pp. 253–269. doi: 10.1007/978-3-030-05542-4_13.

[61] I. Olsen and S. D. Hicks, “Oral microbiota and autism spectrum disorder (ASD),” *Journal of Oral Microbiology*, vol. 12, no. 1. Taylor and Francis Ltd., Jan. 01, 2020. doi: 10.1080/20002297.2019.1702806.

[62] G. F. Ferrazzano, C. Salerno, C. Bravaccio, A. Ingenito, G. Sangianantoni, and T. Cantile, “Autism spectrum disorders and oral health status: Review of the literature,” *Eur J Paediatr Dent*, vol. 21, no. 1, pp. 9–12, 2020, doi: 10.23804/ejpd.2020.21.01.02.

[63] M. C. Cenit, I. C. Nuevo, P. Codoñer-Franch, T. G. Dinan, and Y. Sanz, “Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition,” *European Child and Adolescent Psychiatry*, vol. 26, no. 9. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG, pp. 1081–1092, Sep. 01, 2017. doi: 10.1007/s00787-017-0969-z.

[64] N. Boonchooduang, O. Louthrenoo, N. Chattipakorn, and S. C. Chattipakorn, “Possible links between gut–microbiota and attention-deficit/hyperactivity disorders in children and adolescents,” *European Journal of Nutrition*, vol. 59, no. 8. Springer Science and Business Media Deutschland GmbH, pp. 3391–3403, Dec. 01, 2020. doi: 10.1007/s00394-020-02383-1.

[65] S. Bull-Larsen and M. Hasan Mohajeri, “The potential influence of the bacterial microbiome on the development and progression of adhd,” *Nutrients*, vol. 11, no. 11. MDPI AG, Nov. 01, 2019. doi: 10.3390/nu11112805.

[66] C. de Caro *et al.*, “Can we ‘seize’ the gut microbiota to treat epilepsy?,” *Neuroscience and Biobehavioral Reviews*, vol. 107. Elsevier Ltd, pp. 750–764, Dec. 01, 2019. doi: 10.1016/j.neubiorev.2019.10.002.

[67] J. Wu, Y. Zhang, H. Yang, Y. Rao, J. Miao, and X. Lu, “Intestinal Microbiota as an Alternative Therapeutic Target for Epilepsy,” *Canadian Journal of Infectious Diseases and Medical Microbiology*, vol. 2016, 2016, doi: 10.1155/2016/9032809.

[68] M. Holmes *et al.*, “Cross talk between drug-resistant epilepsy and the gut microbiome,” *Epilepsia*, vol. 61, no. 12. Blackwell Publishing Inc., pp. 2619–2628, Dec. 01, 2020. doi: 10.1111/epi.16744.

[69] G. R. Lum, C. A. Olson, and E. Y. Hsiao, “Emerging roles for the intestinal microbiome in epilepsy,” *Neurobiology of Disease*, vol. 135. Academic Press Inc., Feb. 01, 2020. doi: 10.1016/j.nbd.2019.104576.

[70] M. Dahlin and S. Prast-Nielsen, “The gut microbiome and epilepsy,” *EBioMedicine*, vol. 44. Elsevier B.V., pp. 741–746, Jun. 01, 2019. doi: 10.1016/j.ebiom.2019.05.024.

[71] I. D'Andrea Meira, T. T. Romão, H. J. P. do Prado, L. T. Krüger, M. E. P. Pires, and P. O. da Conceição, "Ketogenic diet and epilepsy: What we know so far," *Front Neurosci*, vol. 13, no. JAN, 2019, doi: 10.3389/fnins.2019.00005.

[72] M. Ułamek-Kozioł, S. J. Czuczwar, R. Pluta, and S. Januszewski, "Ketogenic diet and epilepsy," *Nutrients*, vol. 11, no. 10. MDPI AG, Oct. 01, 2019. doi: 10.3390/nu11102510.

[73] N. J. Talley, G. J. Holtmann, and A. C. Ford, "Pathophysiology of irritable bowel syndrome," 2016. [Online]. Available: www.thelancet.com/gastrohep

[74] B. K. Rodiño *et al.*, "A Review of Microbiota and Irritable Bowel Syndrome: Future in Therapies", doi: 10.6084/m9.figshare.

[75] J. T. Chang, "Pathophysiology of Inflammatory Bowel Diseases," *New England Journal of Medicine*, vol. 383, no. 27, pp. 2652–2664, Dec. 2020, doi: 10.1056/NEJMra2002697.

[76] K. L. Glassner, B. P. Abraham, and E. M. M. Quigley, "The microbiome and inflammatory bowel disease," *Journal of Allergy and Clinical Immunology*, vol. 145, no. 1, pp. 16–27, Jan. 2020, doi: 10.1016/j.jaci.2019.11.003.

[77] I. Khan *et al.*, "Alteration of gut microbiota in inflammatory bowel disease (IBD): Cause or consequence? IBD treatment targeting the gut microbiome," *Pathogens*, vol. 8, no. 3. MDPI AG, Sep. 01, 2019. doi: 10.3390/pathogens8030126.

[78] J. McIlroy, G. Ianiro, I. Mukhopadhya, R. Hansen, and G. L. Hold, "Review article: the gut microbiome in inflammatory bowel disease—avenues for microbial management," *Alimentary Pharmacology and Therapeutics*, vol. 47, no. 1. Blackwell Publishing Ltd, pp. 26–42, Jan. 01, 2018. doi: 10.1111/apt.14384.

[79] H. S. Lee, E. Lobbestael, S. Vermeire, J. Sabino, and I. Cleynen, "Inflammatory bowel disease and Parkinson's disease: Common pathophysiological links," *Gut*, vol. 70, no. 2. BMJ Publishing Group, pp. 408–417, Feb. 01, 2021. doi: 10.1136/gutjnl-2020-322429.

[80] R. Dobson and G. Giovannoni, "Multiple sclerosis – a review," *European Journal of Neurology*, vol. 26, no. 1. Blackwell Publishing Ltd, pp. 27–40, Jan. 01, 2019. doi: 10.1111/ene.13819.

[81] M. K. Boziki *et al.*, "Microbiome in multiple sclerosis; where are we, what we know and do not know," *Brain Sciences*, vol. 10, no. 4. MDPI AG, Apr. 01, 2020. doi: 10.3390/brainsci10040234.

[82] G. Schepici, S. Silvestro, P. Bramanti, and E. Mazzon, "The Gut Microbiota in Multiple Sclerosis: An Overview of Clinical Trials," *Cell Transplantation*, vol. 28, no. 12. SAGE Publications Ltd, pp. 1507–1527, Dec. 01, 2019. doi: 10.1177/0963689719873890.

[83] L. M. Cox *et al.*, "Gut Microbiome in Progressive Multiple Sclerosis," *Ann Neurol*, vol. 89, no. 6, pp. 1195–1211, Jun. 2021, doi: 10.1002/ana.26084.

[84] T. Zhang, Q. Li, L. Cheng, H. Buch, and F. Zhang, "Akkermansia muciniphila is a promising probiotic," *Microbial Biotechnology*, vol. 12, no. 6. John Wiley and Sons Ltd, pp. 1109–1125, Nov. 01, 2019. doi: 10.1111/1751-7915.13410.

[85] C. R. Camara-Lemarroy, L. Metz, J. B. Meddings, K. A. Sharkey, and V. Wee Yong, "The intestinal barrier in multiple sclerosis: Implications for pathophysiology and therapeutics," *Brain*, vol. 141, no. 7. Oxford University Press, pp. 1900–1916, Jul. 01, 2018. doi: 10.1093/brain/awy131.

[86] D. W. Mielcarz and L. H. Kasper, “The Gut Microbiome in Multiple Sclerosis,” *Current Treatment Options in Neurology*, vol. 17, no. 4. Current Science Inc., Apr. 01, 2015. doi: 10.1007/s11940-015-0344-7.
[87] L. A. Gerdes, H. Yoon, and A. Peters, “Microbiota and multiple sclerosis,” *Nervenarzt*, vol. 91, no. 12. Springer Medizin, pp. 1096–1107, Dec. 01, 2020. doi: 10.1007/s00115-020-01012-w.
[88] B. Parodi and N. Kerlero de Rosbo, “The Gut-Brain Axis in Multiple Sclerosis. Is Its Dysfunction a Pathological Trigger or a Consequence of the Disease?,” *Frontiers in Immunology*, vol. 12. Frontiers Media S.A., Sep. 21, 2021. doi: 10.3389/fimmu.2021.718220.
[89] T. Kirby and J. Ochoa-Repáraz, “The Gut Microbiome in Multiple Sclerosis: A Potential Therapeutic Avenue,” *Medical Sciences*, vol. 6, no. 3, p. 69, Aug. 2018, doi: 10.3390/medsci6030069.
[90] “Role of Gut Microbiota in Rheumatoid Arthritis | Enhanced Reader.”
[91] X. Wu *et al.*, “Molecular insight into gut microbiota and rheumatoid arthritis,” *International Journal of Molecular Sciences*, vol. 17, no. 3. MDPI AG, Mar. 22, 2016. doi: 10.3390/ijms17030431.
[92] G. Horta-Baas, M. D. S. Romero-Figueroa, A. J. Montiel-Jarquín, M. L. Pizano-Zárate, J. García-Mena, and N. Ramírez-Durán, “Intestinal Dysbiosis and Rheumatoid Arthritis: A Link between Gut Microbiota and the Pathogenesis of Rheumatoid Arthritis,” *Journal of Immunology Research*, vol. 2017. Hindawi Limited, 2017. doi: 10.1155/2017/4835189.
[93] M. du Teil Espina, G. Gabarrini, H. J. M. Harmsen, J. Westra, A. J. van Winkelhoff, and J. M. van Dijl, “Talk to your gut: The oral-gut microbiome axis and its immunomodulatory role in the etiology of rheumatoid arthritis,” *FEMS Microbiology Reviews*, vol. 43, no. 1. Oxford University Press, pp. 1–18, Jan. 01, 2019. doi: 10.1093/femsre/fuy035.
[94] A. S. Bergot, R. Giri, and R. Thomas, “The microbiome and rheumatoid arthritis,” *Best Practice and Research: Clinical Rheumatology*. Bailliere Tindall Ltd, 2020. doi: 10.1016/j.berh.2020.101497.
[95] M. M. Zaiss, H. J. Joyce Wu, D. Mauro, G. Schett, and F. Ciccia, “The gut–joint axis in rheumatoid arthritis,” *Nature Reviews Rheumatology*, vol. 17, no. 4. Nature Research, pp. 224–237, Apr. 01, 2021. doi: 10.1038/s41584-021-00585-3.
[96] Y. Maeda and K. Takeda, “Host–microbiota interactions in rheumatoid arthritis,” *Experimental and Molecular Medicine*, vol. 51, no. 12. Springer Nature, Dec. 01, 2019. doi: 10.1038/s12276-019-0283-6.
[97] H. Xu *et al.*, “Interactions between Gut Microbiota and Immunomodulatory Cells in Rheumatoid Arthritis,” *Mediators of Inflammation*, vol. 2020. Hindawi Limited, 2020. doi: 10.1155/2020/1430605.
[98] Y. Kang, Y. Cai, X. Zhang, X. Kong, and J. Su, “Darmmikrobiota und rheumatoide Arthritis: von der Pathogenese zu neuen therapeutischen Strategien,” *Z Rheumatol*, vol. 76, no. 5, pp. 451–457, Jun. 2017, doi: 10.1007/s00393-016-0237-5.
[99] “Role of Gut Microbiota in Rheumatoid Arthritis | Enhanced Reader.”
[100] R. Bodkhe, B. Balakrishnan, and V. Taneja, “The role of microbiome in rheumatoid arthritis treatment,” *Therapeutic Advances in Musculoskeletal Disease*, vol. 11. SAGE Publications Ltd, 2019. doi: 10.1177/1759720X19844632.

[101] T. Kitai and W. H. W. Tang, “Gut microbiota in cardiovascular disease and heart failure,” *Clinical Science*, vol. 132, no. 1. Portland Press Ltd, pp. 85–91, 2018. doi: 10.1042/cs20171090.
[102] Y. Zhao and Z. Wang, “Gut microbiome and cardiovascular disease,” *Current Opinion in Cardiology*, vol. 35, no. 3. Lippincott Williams and Wilkins, pp. 207–218, 2020. doi: 10.1097/HCO.0000000000000720.
[103] A. F. Ahmad, G. Dwivedi, F. O’gara, J. Caparros-Martin, and N. C. Ward, “The gut microbiome and cardiovascular disease: current knowledge and clinical potential,” *Am J Physiol Heart Circ Physiol*, vol. 317, pp. 923–938, 2019, doi: 10.1152/ajpheart.00376.2019.-Cardiovascular.
[104] E. Sanchez-Rodriguez *et al.*, “The gut microbiota and its implication in the development of atherosclerosis and related cardiovascular diseases,” *Nutrients*, vol. 12, no. 3. MDPI AG, Mar. 01, 2020. doi: 10.3390/nu12030605.
[105] B. J. H. Verhaar, A. Prodan, M. Nieuwdorp, and M. Muller, “Gut microbiota in hypertension and atherosclerosis: A review,” *Nutrients*, vol. 12, no. 10, pp. 1–22, Oct. 2020, doi: 10.3390/nu12102982.
[106] W. H. W. Tang, D. Y. Li, and S. L. Hazen, “Dietary metabolism, the gut microbiome, and heart failure,” *Nature Reviews Cardiology*, vol. 16, no. 3. Nature Publishing Group, pp. 137–154, Mar. 01, 2019. doi: 10.1038/s41569-018-0108-7.
[107] W. H. W. Tang, F. Bäckhed, U. Landmesser, and S. L. Hazen, “Intestinal Microbiota in Cardiovascular Health and Disease: JACC State-of-the-Art Review,” *Journal of the American College of Cardiology*, vol. 73, no. 16. Elsevier USA, pp. 2089–2105, Apr. 30, 2019. doi: 10.1016/j.jacc.2019.03.024.
[108] M. Witkowski, T. L. Weeks, and S. L. Hazen, “Gut Microbiota and Cardiovascular Disease,” *Circulation Research*, vol. 127, no. 4. Lippincott Williams and Wilkins, pp. 553–570, Jul. 31, 2020. doi: 10.1161/CIRCRESAHA.120.316242.
[109] J. Peng, X. Xiao, M. Hu, and X. Zhang, “Interaction between gut microbiome and cardiovascular disease,” *Life Sciences*, vol. 214. Elsevier Inc., pp. 153–157, Dec. 01, 2018. doi: 10.1016/j.lfs.2018.10.063.
[110] Z. Wang and Y. Zhao, “Gut microbiota derived metabolites in cardiovascular health and disease,” *Protein and Cell*, vol. 9, no. 5. Higher Education Press, pp. 416–431, May 01, 2018. doi: 10.1007/s13238-018-0549-0.
[111] N. Kazemian, M. Mahmoudi, F. Halperin, J. C. Wu, and S. Pakpour, “Gut microbiota and cardiovascular disease: Opportunities and challenges,” *Microbiome*, vol. 8, no. 1. BioMed Central Ltd., Mar. 14, 2020. doi: 10.1186/s40168-020-00821-0.
[112] W. H. W. Tang and S. L. Hazen, “The contributory role of gut microbiota in cardiovascular disease,” *Journal of Clinical Investigation*, vol. 124, no. 10. American Society for Clinical Investigation, pp. 4204–4211, Oct. 01, 2014. doi: 10.1172/JCI72331.
[113] H. S. Nam, “Gut microbiota and ischemic stroke: The role of trimethylamine N-oxide,” *Journal of Stroke*, vol. 21, no. 2. Korean Stroke Society, pp. 151–159, May 01, 2019. doi: 10.5853/jos.2019.00472.
[114] R. L. Sacco *et al.*, “An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association,” *Stroke*, vol. 44, no. 7, pp. 2064–2089, 2013, doi: 10.1161/STR.0b013e318296aeca.

[115] R. Pluta, S. Januszewski, and S. J. Czuczwar, “The role of gut microbiota in an ischemic stroke,” *International Journal of Molecular Sciences*, vol. 22, no. 2. MDPI AG, pp. 1–11, Jan. 02, 2021. doi: 10.3390/ijms22020915.
[116] A. Arya and B. Hu, “Brain–gut axis after stroke,” *Brain Circ*, vol. 4, no. 4, p. 165, 2018, doi: 10.4103/bc.bc_32_18.
[117] D. J. Durgan, J. Lee, L. D. McCullough, and R. M. Bryan, “Examining the Role of the Microbiota-Gut-Brain Axis in Stroke,” *Stroke*, vol. 50, no. 8. Lippincott Williams and Wilkins, pp. 2270–2277, Aug. 01, 2019. doi: 10.1161/STROKEAHA.119.025140.
[118] K. Winek, U. Dirnagl, and A. Meisel, “The Gut Microbiome as Therapeutic Target in Central Nervous System Diseases: Implications for Stroke,” *Neurotherapeutics*, vol. 13, no. 4. Springer New York LLC, pp. 762–774, Oct. 01, 2016. doi: 10.1007/s13311-016-0475-x.
[119] M. Gurung *et al.*, “Role of gut microbiota in type 2 diabetes pathophysiology,” *EBioMedicine*, vol. 51. Elsevier B.V., Jan. 01, 2020. doi: 10.1016/j.ebiom.2019.11.051.
[120] A. Sircana *et al.*, “Altered Gut Microbiota in Type 2 Diabetes: Just a Coincidence?,” *Current Diabetes Reports*, vol. 18, no. 10. Current Medicine Group LLC 1, Oct. 01, 2018. doi: 10.1007/s11892-018-1057-6.
[121] M. K. Salgaço, L. G. S. Oliveira, G. N. Costa, F. Bianchi, and K. Sivieri, “Relationship between gut microbiota, probiotics, and type 2 diabetes mellitus,” *Applied Microbiology and Biotechnology*, vol. 103, no. 23–24. Springer, pp. 9229–9238, Dec. 01, 2019. doi: 10.1007/s00253-019-10156-y.
[122] D. M. Tanase *et al.*, “Role of gut microbiota on onset and progression of microvascular complications of type 2 diabetes (T2DM),” *Nutrients*, vol. 12, no. 12. MDPI AG, pp. 1–26, Dec. 01, 2020. doi: 10.3390/nu12123719.
[123] E. E. Patterson *et al.*, “Gut microbiota, obesity and diabetes,” *Postgraduate Medical Journal*, vol. 92, no. 1087. BMJ Publishing Group, pp. 286–300, May 01, 2016. doi: 10.1136/postgradmedj-2015-133285.
[124] G. Yang *et al.*, “Role of the gut microbiota in type 2 diabetes and related diseases,” *Metabolism: Clinical and Experimental*, vol. 117. W.B. Saunders, Apr. 01, 2021. doi: 10.1016/j.metabol.2021.154712.
[125] G. Blandino, R. Inturri, F. Lazzara, M. di Rosa, and L. Malaguarnera, “Impact of gut microbiota on diabetes mellitus,” *Diabetes and Metabolism*, vol. 42, no. 5. Elsevier Masson SAS, pp. 303–315, Nov. 01, 2016. doi: 10.1016/j.diabet.2016.04.004.
[126] A. Everard and P. D. Cani, “Diabetes, obesity and gut microbiota,” *Best Practice and Research: Clinical Gastroenterology*, vol. 27, no. 1. Bailliere Tindall Ltd, pp. 73–83, 2013. doi: 10.1016/j.bpg.2013.03.007.
[127] A. Pascale, N. Marchesi, S. Govoni, A. Coppola, and C. Gazzaruso, “The role of gut microbiota in obesity, diabetes mellitus, and effect of metformin: new insights into old diseases,” *Current Opinion in Pharmacology*, vol. 49. Elsevier Ltd, pp. 1–5, Dec. 01, 2019. doi: 10.1016/j.coph.2019.03.011.
[128] O. A. Baothman, M. A. Zamzami, I. Taher, J. Abubaker, and M. Abu-Farha, “The role of Gut Microbiota in the development of obesity and Diabetes,” *Lipids in Health and Disease*, vol. 15, no. 1. BioMed Central Ltd., Jun. 18, 2016. doi: 10.1186/s12944-016-0278-4.
[129] H. Han *et al.*, “Gut microbiota and type 1 diabetes,” *International Journal of Molecular Sciences*, vol. 19, no. 4. MDPI AG, Apr. 01, 2018. doi: 10.3390/ijms19040995.

[130] N. G. Vallianou, T. Stratigou, and S. Tsagarakis, “Metformin and gut microbiota: their interactions and their impact on diabetes,” *Hormones*, vol. 18, no. 2. Springer, pp. 141–144, Jun. 01, 2019. doi: 10.1007/s42000-019-00093-w.
[131] A. ver Heul, J. Planer, and A. L. Kau, “The Human Microbiota and Asthma,” *Clinical Reviews in Allergy and Immunology*, vol. 57, no. 3. Humana Press Inc., pp. 350–363, Dec. 01, 2019. doi: 10.1007/s12016-018-8719-7.
[132] F. Frati *et al.*, “The role of the microbiome in asthma: The gut–lung axis,” *International Journal of Molecular Sciences*, vol. 20, no. 1. MDPI AG, Jan. 01, 2019. doi: 10.3390/ijms20010123.
[133] A. Riiser, “The human microbiome, asthma, and allergy,” *Allergy, Asthma and Clinical Immunology*, vol. 11, no. 1. BioMed Central Ltd., Dec. 10, 2015. doi: 10.1186/s13223-015-0102-0.
[134] K. E. Fujimura and S. v. Lynch, “Microbiota in allergy and asthma and the emerging relationship with the gut microbiome,” *Cell Host and Microbe*, vol. 17, no. 5. Cell Press, pp. 592–602, May 13, 2015. doi: 10.1016/j.chom.2015.04.007.
[135] D. Zhang, S. Li, N. Wang, H. Y. Tan, Z. Zhang, and Y. Feng, “The Cross-Talk Between Gut Microbiota and Lungs in Common Lung Diseases,” *Frontiers in Microbiology*, vol. 11. Frontiers Media S.A., Feb. 25, 2020. doi: 10.3389/fmicb.2020.00301.
[136] K. Hufnagl, I. Pali-Schöll, F. Roth-Walter, and E. Jensen-Jarolim, “Dysbiosis of the gut and lung microbiome has a role in asthma,” *Seminars in Immunopathology*, vol. 42, no. 1. Springer, pp. 75–93, Feb. 01, 2020. doi: 10.1007/s00281-019-00775-y.
[137] W. Barcik, R. C. T. Boutin, M. Sokolowska, and B. B. Finlay, “The Role of Lung and Gut Microbiota in the Pathology of Asthma,” *Immunity*, vol. 52, no. 2. Cell Press, pp. 241–255, Feb. 18, 2020. doi: 10.1016/j.immuni.2020.01.007.
[138] M. Sokolowska, R. Frei, N. Lunjani, C. A. Akdis, and L. O’Mahony, “Microbiome and asthma,” *Asthma Res Pract*, vol. 4, no. 1, Dec. 2018, doi: 10.1186/s40733-017-0037-y.
[139] L. Chunxi, L. Haiyue, L. Yanxia, P. Jianbing, and S. Jin, “The Gut Microbiota and Respiratory Diseases: New Evidence,” *Journal of Immunology Research*, vol. 2020. Hindawi Limited, 2020. doi: 10.1155/2020/2340670.
[140] Y. J. Huang and H. A. Boushey, “The microbiome in asthma,” *Journal of Allergy and Clinical Immunology*, vol. 135, no. 1, pp. 25–30, Jan. 2015, doi: 10.1016/j.jaci.2014.11.011.
[141] G. L. V. de Oliveira, C. N. S. Oliveira, C. F. Pinzan, L. V. V. de Salis, and C. R. de B. Cardoso, “Microbiota Modulation of the Gut-Lung Axis in COVID-19,” *Frontiers in Immunology*, vol. 12. Frontiers Media S.A., Feb. 24, 2021. doi: 10.3389/fimmu.2021.635471.
[142] D. Dhar and A. Mohanty, “Gut microbiota and Covid-19- possible link and implications,” *Virus Research*, vol. 285. Elsevier B.V., Aug. 01, 2020. doi: 10.1016/j.virusres.2020.198018.
[143] S. Rajput, D. Paliwal, M. Naithani, A. Kothari, K. Meena, and S. Rana, “COVID-19 and Gut Microbiota: A Potential Connection,” *Indian Journal of Clinical Biochemistry*, vol. 36, no. 3. Springer, pp. 266–277, Jul. 01, 2021. doi: 10.1007/s12291-020-00948-9.
[144] A. Akour, “Probiotics and COVID-19: is there any link?,” *Letters in Applied Microbiology*, vol. 71, no. 3. Blackwell Publishing Ltd, pp. 229–234, Sep. 01, 2020. doi: 10.1111/lam.13334.
[145] S. Donati Zeppa, D. Agostini, G. Piccoli, V. Stocchi, and P. Sestili, “Gut Microbiota Status in COVID-19: An Unrecognized Player?,” *Frontiers in Cellular and Infection*

Microbiology, vol. 10. Frontiers Media S.A., Nov. 26, 2020. doi: 10.3389/fcimb.2020.576551.

[146] W. Li, Y. Deng, Q. Chu, and P. Zhang, "Gut microbiome and cancer immunotherapy," *Cancer Letters*, vol. 447. Elsevier Ireland Ltd, pp. 41–47, Apr. 10, 2019. doi: 10.1016/j.canlet.2019.01.015.

[147] V. Gopalakrishnan, B. A. Helmink, C. N. Spencer, A. Reuben, and J. A. Wargo, "The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy," *Cancer Cell*, vol. 33, no. 4. Cell Press, pp. 570–580, Apr. 09, 2018. doi: 10.1016/j.ccell.2018.03.015.

[148] C. B. Zhou, Y. L. Zhou, and J. Y. Fang, "Gut Microbiota in Cancer Immune Response and Immunotherapy," *Trends in Cancer*, vol. 7, no. 7. Cell Press, pp. 647–660, Jul. 01, 2021. doi: 10.1016/j.trecan.2021.01.010.

[149] S. Vivarelli *et al.*, "Gut microbiota and cancer: From pathogenesis to therapy," *Cancers*, vol. 11, no. 1. MDPI AG, Jan. 01, 2019. doi: 10.3390/cancers11010038.

[150] S. Gori *et al.*, "Gut microbiota and cancer: How gut microbiota modulates activity, efficacy and toxicity of antitumoral therapy," *Critical Reviews in Oncology/Hematology*, vol. 143. Elsevier Ireland Ltd, pp. 139–147, Nov. 01, 2019. doi: 10.1016/j.critrevonc.2019.09.003.

[151] W. Y. Cheng, C. Y. Wu, and J. Yu, "The role of gut microbiota in cancer treatment: Friend or foe?," *Gut*, vol. 69, no. 10. BMJ Publishing Group, pp. 1867–1876, Oct. 01, 2020. doi: 10.1136/gutjnl-2020-321153.

[152] E. M. Park, M. Chelvanambi, N. Bhutiani, G. Kroemer, L. Zitvogel, and J. A. Wargo, "Targeting the gut and tumor microbiota in cancer," *Nature Medicine*, vol. 28, no. 4. Nature Research, pp. 690–703, Apr. 01, 2022. doi: 10.1038/s41591-022-01779-2.

[153] S. H. Wong, T. N. Y. Kwong, C. Y. Wu, and J. Yu, "Clinical applications of gut microbiota in cancer biology," *Seminars in Cancer Biology*, vol. 55. Academic Press, pp. 28–36, Apr. 01, 2019. doi: 10.1016/j.semcancer.2018.05.003.

[154] W. Ma, Q. Mao, W. Xia, G. Dong, C. Yu, and F. Jiang, "Gut microbiota shapes the efficiency of cancer therapy," *Frontiers in Microbiology*, vol. 10, no. JUN. Frontiers Media S.A., 2019. doi: 10.3389/fmicb.2019.01050.

[155] P. Guo, K. Zhang, X. Ma, and P. He, "Clostridium species as probiotics: Potentials and challenges," *Journal of Animal Science and Biotechnology*, vol. 11, no. 1. BioMed Central Ltd, Feb. 20, 2020. doi: 10.1186/s40104-019-0402-1.

[156] M. K. Stoeva *et al.*, "Butyrate-producing human gut symbiont, Clostridium butyricum, and its role in health and disease," *Gut Microbes*, vol. 13, no. 1. Bellwether Publishing, Ltd., pp. 1–28, 2021. doi: 10.1080/19490976.2021.1907272.

[157] T. Ariyoshi, M. Hagihara, M. Takahashi, and H. Mikamo, "Effect of Clostridium butyricum on Gastrointestinal Infections," *Biomedicines*, vol. 10, no. 2. MDPI, Feb. 01, 2022. doi: 10.3390/biomedicines10020483.

[158] N. Cassir, S. Benamar, and B. la Scola, "Clostridium butyricum: From beneficial to a new emerging pathogen," *Clinical Microbiology and Infection*, vol. 22, no. 1. Elsevier B.V., pp. 37–45, Jan. 01, 2016. doi: 10.1016/j.cmi.2015.10.014.

[159] P. Sossai, "Butyric acid: What is the future for this old substance?," *Swiss Medical Weekly*, vol. 142, no. JUNE. Jun. 2012. doi: 10.4414/smw.2012.13596.

[160] T. Banasiewicz, D. Domagalska, K. Borycka-Kiciak, and G. Rydzewska, "Determination of butyric acid dosage based on clinical and experimental studies-a literature review,"

Przeglad Gastroenterologiczny, vol. 15, no. 2. Termedia Publishing House Ltd., pp. 119–125, 2020. doi: 10.5114/pg.2020.95556.

[161] Q. Zhai, S. Feng, N. Arjan, and W. Chen, "A next generation probiotic, Akkermansia muciniphila," *Critical Reviews in Food Science and Nutrition*, vol. 59, no. 19. Taylor and Francis Inc., pp. 3227–3236, Oct. 28, 2019. doi: 10.1080/10408398.2018.1517725.

[162] P. D. Cani and W. M. de Vos, "Next-generation beneficial microbes: The case of Akkermansia muciniphila," *Frontiers in Microbiology*, vol. 8, no. SEP. Frontiers Media S.A., Sep. 22, 2017. doi: 10.3389/fmicb.2017.01765.

[163] S. Y. Geerlings, I. Kostopoulos, W. M. de Vos, and C. Belzer, "Akkermansia muciniphila in the human gastrointestinal tract: When, where, and how?," *Microorganisms*, vol. 6, no. 3. MDPI AG, Jul. 23, 2018. doi: 10.3390/microorganisms6030075.

[164] "Akkermansia muciniphila: key player in metabolic and gastrointestinal disorders."

[165] Y. Naito, K. Uchiyama, and T. Takagi, "A nexttgeneration beneficial microbe: Akkermansia muciniphila," *J. Clin. Biochem. Nutr*, vol. 63, no. 1, pp. 33–35, 2018, doi: 10.3164/jcbn.18857.

[166] M. Derrien, C. Belzer, and W. M. de Vos, "Akkermansia muciniphila and its role in regulating host functions," *Microbial Pathogenesis*, vol. 106. Academic Press, pp. 171–181, May 01, 2017. doi: 10.1016/j.micpath.2016.02.005.

[167] K. R. Pandey, S. R. Naik, and B. v. Vakil, "Probiotics, prebiotics and synbiotics- a review," *Journal of Food Science and Technology*, vol. 52, no. 12. Springer India, pp. 7577–7587, Dec. 01, 2015. doi: 10.1007/s13197-015-1921-1.

[168] L. K. Sarao and M. Arora, "Probiotics, prebiotics, and microencapsulation: A review," *Crit Rev Food Sci Nutr*, vol. 57, no. 2, pp. 344–371, Jan. 2017, doi: 10.1080/10408398.2014.887055.

[169] U. Vyas and N. Ranganathan, "Probiotics, prebiotics, and synbiotics: Gut and beyond," *Gastroenterology Research and Practice*. 2012. doi: 10.1155/2012/872716.

[170] R. George Kerry, J. K. Patra, S. Gouda, Y. Park, H. S. Shin, and G. Das, "Benefaction of probiotics for human health: A review," *Journal of Food and Drug Analysis*, vol. 26, no. 3. Elsevier Taiwan LLC, pp. 927–939, Jul. 01, 2018. doi: 10.1016/j.jfda.2018.01.002.

[171] H. Antushevich, "Fecal microbiota transplantation in disease therapy," *Clinica Chimica Acta*, vol. 503. Elsevier B.V., pp. 90–98, Apr. 01, 2020. doi: 10.1016/j.cca.2019.12.010.

[172] N. M. J. Hanssen, W. M. de Vos, and M. Nieuwdorp, "Fecal microbiota transplantation in human metabolic diseases: From a murky past to a bright future?," *Cell Metabolism*, vol. 33, no. 6. Cell Press, pp. 1098–1110, Jun. 01, 2021. doi: 10.1016/j.cmet.2021.05.005.

[173] R. E. Ooijevaar, E. M. Terveer, H. W. Verspaget, E. J. Kuijper, and J. J. Keller, "Annual Review of Medicine Clinical Application and Potential of Fecal Microbiota Transplantation," *Annu. Rev. Med*, vol. 70, pp. 335–51, 2019, doi: 10.1146/annurev-med-111717.

[174] S. Gupta, E. Allen-Vercoe, and E. O. Petrof, "Fecal microbiota transplantation: In perspective," *Therapeutic Advances in Gastroenterology*, vol. 9, no. 2. SAGE Publications Ltd, pp. 229–239, Mar. 01, 2016. doi: 10.1177/1756283X15607414.

[175] K. O. Kim and M. Gluck, "Fecal microbiota transplantation: An update on clinical practice," *Clinical Endoscopy*, vol. 52, no. 2. Korean Society of Gastrointestinal Endoscopy, pp. 137–143, 2019. doi: 10.5946/CE.2019.009.