DOI: https://doi.org/10.53350/pjmhs2023175311

ORIGINAL ARTICLE

Gut Microbiome and its Role in the Development of Neurological Disorder (Schizophrenia)

AYESHA AMEEN[1], MUHAMMAD NADEEM AKRAM[2], SANA FAROOQ[3], MEHREEN FATIMA[4], HASSAN RAZA[4], RABIA NAZ[4], UMER AZIZ[5], MARIYAM AZIZ[4], SYED TAHIR[5], ATHAR HUSSAIN[6]

[1]*Office of Research Innovation and Commercialization, University of Management and Technology*
[2]*Riphah International University Faisalabad, Pakistan*
[2]*Institute of biology Leidon University, the Netherlands*
[3]*University of Salford, Manchester, UK*
[4]*Department of Life Sciences, University of Management and Technology*
[5]*Akhtar Saeed Medical College, Bahria International Hospital, Lahore*
[6]*Genomics Lab, Department of Food Science and Technology, School of Food and Agricultural Sciences (SFAS), University of Management and Technology (UMT), Lahore, Pakistan*
Corresponding author Athar Hussain, Email: athar.hussain@umt.edu.pk

ABSTRACT

Purpose: The gut microbiome, defined as the community of microorganisms residing in the digestive tract, is believed to play a crucial role in the development of neurological disorders, including schizophrenia.

Design: Recent research indicates that individuals with schizophrenia have altered gut microbiomes, characterized by reduced levels of beneficial bacteria such as Bifidobacterium and Lactobacillus, and increased levels of potentially harmful bacteria, such as Proteobacteria.

Findings: Furthermore, studies show that the communication between the gut and the brain, known as the gut-brain axis, is disrupted in individuals with schizophrenia. While the exact mechanisms underlying the association between the gut microbiome and schizophrenia are not yet fully understood, researchers suggest that changes in the gut microbiome may affect the immune system and neurotransmitters, which in turn contribute to the development of the disorder

Practical Implication: Targeting the gut microbiome through interventions like probiotics and the Mediterranean diet may offer a promising therapeutic approach for individuals with schizophrenia.

Conclusion: However, more research is needed to fully comprehend the complex interplay between the gut microbiome and schizophrenia, including the specific mechanisms by which the gut microbiome contributes to the development of the disorder.

Keywords: Gut Microbiome. Microbiota, Immune cells, Schizophrenia

INTRODUCTION

The human body hosts a variety of metabolic reactions that contribute to immune system development, detoxification, and digestion. In addition to the inherited genome, the body also acquires a microbiome from the environment [1]. While the inherited genome remains constant throughout an individual's life, the microbiome is highly changeable and affected by factors such as age, diet, exercise, hormonal cycles, and therapies. The gut microbiome is composed of various phyla, including firmicutes, Bacteroides, actinobacteria, and proteobacteria. High levels of bacteria can be found in the intestinal lumen and fecal samples. The gut microbiome can be altered by food, probiotics, prebiotics, and antibiotics, and these changes have been associated with gastrointestinal and chronic diseases. Recent research has shown a link between gut microbial diversity and psychiatric disorders such as major depressive disorder, schizophrenia, bipolar disorder, and autism spectrum disorder [2,3]. Patients with depression have shown changes in microbiome diversity, while patients with bipolar disorder have been linked to high levels of Coriobacteriaceae and low levels of Faecalibacterium. Schizophrenia has also been linked to disruptions in the gut-brain axis, and the gut microbiome of schizophrenia patients differs from that of healthy individuals. The microbiota's diversity varies from person to person and is influenced by environmental factors [4,5]. Microbiome modulators such as prebiotics and probiotics have been developed to correct dysbiosis and restore gut function, which may provide valuable insights into the diagnosis and prognosis of psychiatric disorders. Further research is necessary to better understand the relationship between the gut microbiome and psychiatric disorders in different populations without resorting to plagiarism [6].

Maturation and development of gut microbiome: A series of critical windows of opportunities for healthy development of gut microbiome is started from conception to child's second birthday. This period is important for human body to develop important foundations for long term health. The interaction and communication process in human biology is driven by abiotic and biotic environment [7]. A diversified microbial community is present in a close proximity and share same habitat of gut is referred to as gut microbiome. It is composed of microbial diversity of bacteria, archea and protozoa which release different components e.g metabolites and mobile genetic elements (e.g transposones).The microbial diversity and production of metabolites in maintained balance habitat makes healthy gut ecology. Clinical observations evident the main disrupter of microbiome in children and adults, one disruptor is antibiotic and other is modulator (nutrition or diet). Gnobiotic animal experiments are required to find details of gut microbiome disruption in infants and children which can lead to many neurodevelopment and chronic diseases. Gut and brain interacts in different terms and this communication is referred to as gut brain axis, many scientists have worked on this interaction of brain with gut. In this condition, Microbial diversity plays a very important role to give signals for metabolites production and immune response. This gut brain axis interaction and microbiota develops individual's behavior [8]. Experimental Studies on animal model clearly evident that the effect of gut microbiota on neurochemical metabolism and gene expression is highly impacting on behavior and performance of subjects. Based on these changes, a modulating role of the gut microbiota has been demonstrated for a variety of neuropsychiatric disorders, including depression, anxiety, and movement including Parkinson's, and importantly for the pediatric population autism. The way in which organisms that live in the gut influence the central nervous system (CNS) and host behavior is likely to be multifactorial in origin. This includes immunologic, endocrine, and metabolic mechanisms, all of which are pathways used for other microbial–host interactions [9]. Research on working with germ free mice and conventionally raised mice demonstrated that GF mice was observed in more proper normal behavior development on stress related and anxiety related responses. GF condition cannot be applicable on human beings so it is very common to develop certain neuropsychiatric disorder in early development of gut and brain axis. Food and gut environment plays an important role in shaping microbiota diversity and host immunity. Gut microbiome in mammals have co-evolved and co-adapted an inseparable relationship. This natural relationship of gut bacteria with metabolism and nutrition has also been considered a milestone in to fight against infectious diseases.

Recently, the advances in the study of the effect of antibiotics on the gut microbiome have raised many queries about its dysbiosis. Many antibiotics have different effects on the severity of microbial community disruption in the gut. It also has opened up the value of gut microbiome restoration, the unfavorable effects of antibiotics treatments, and the reversal of its adversity that need proper care and time to restore. The gut is the largest reservoir of microbes; a limitation to the study of bacterial identification is the use of conventional cultural techniques [10]. Many of the microbes are not identifiable by using simple cultural techniques, special emphasis needs to be put on the anaerobic bacteria that are not easy to culture by standard methods. Recent advancements in culturing techniques along with advances in metagenomics and proteomics have opened up a new direction of composition function and restoration of bacterial community exploited by antibiotics treatment. Bacteria are still considered as important participants in maintaining homeostasis but fungi, phage, virus, and protozoa are also identified in gut functioning. Five major bacterial phyla in the gut are Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia, accounting for more than 90% of the total bacterial population that inhabit the gut. The rest of the bacteria are from less abundant phyla, such as Fusobacteria and Fibrobacteres [11]. These prevalent microbial species reside in different segments of the gut and perform different tasks and also participate in a physiological processes. The main task of these gut microbes is to maintain and regulate the immune system, utilizing food and its digestion, and synthesis of essential amino acids required in the human body. Thousands of natural substances are used to synthesize antibiotics. The produced antibiotics are extensively used to save humans from many pathogenic diseases. However, excessive use of these antibiotics has raised many health issues related to the gut microbiome. They are considered to be the main issue of gut microbiome dysbiosis by causing many neurological and chronic diseases like depression autism, diabetes, inflammatory bowel disease, arthritis, and superinfections in severely ill patients [12]. Antibiotics can affect gut microbiota in different ways, directly or indirectly, their association is direct with the depletion of pathogenic bacteria but their broad-spectrum activities lead to disrupting the commensal bacterial species in gut resulting in worst circumstances for the gut to function properly [13]. Antibiotics combination have different antimicrobial spectra and result in different changes in the gut microbiome, vancomycin is decreasing fecal microbial diversity absolute numbers of gram-positive bacteria from the firmicutes phylum are also decreased [14]. A combination of antibiotics containing ampicillin, gentamycin, and neomycin not only decreases the number of beneficial bacteria in the gut but also shifts the composition of the gut microbiome [15]. Whenever a scientist wants to study the effect of used antibiotics on microbiota on host health, first thing is to understand the relation of a particular antibiotic with the reshaping of specific gut bacteria. An increase in the use of antibiotics has rapidly disseminated bacterial-resistant genes [16]. Under selective pressure by antibiotics, sensitive strains will be eliminated, giving the antibiotic-resistant strains a growth advantage. The percentage of horizontally transferred antibiotic resistance genes is approximately 6 percent which is 4.8 percent higher than transmitted antimicrobial peptide resistance genes. Antibiotics have also an effect on the production of metabolites in host cells and alter the signal transmittance in host cells e.g epithelial and immune cells are the major victims of these alterations. Depletion of commensal bacteria from the gut results in less fermentation of fiber to produce short-chain fatty acids in the large intestine can also lead to inflammatory disease [17]. Clostridium difficile, a spore-forming gram-positive anaerobic bacteria and the leading cause of antibiotic-associated diarrhea, is significantly inhibited by secondary bile acids. A combination of cefoperazone, clindamycin, and vancomycin is associated with the loss of Lachnospiraceae and Ruminococcaceae families and a reduced transformation of primary bile acids to secondary bile acids in the large intestine, increasing the risk of C. difficile infection. Antibiotic-induced alteration in amino acid production and increased amount of proline in the gut can also deplete C. difficile [18].

Another clinical study on antibiotics consumption elaborated that oral antibiotics have also been used to examine the contribution of the maternal gut microbiota during pregnancy to offspring behavior by maternal treatment either preconception (non-absorbable sulfonamide) or early in gestation (neomycin, pimaricin, bacitracin) [19]. Compared to controls, offspring of antibiotic-treated mothers demonstrated increased anxiety-like behaviors and diminished social interactions. Analysis of fecal samples from antibiotic-exposed offspring demonstrated a 50% decrease in the relative abundance of the order Lactobacillales and increase in the bacterial family Clostridium. The behavioral phenotypes in offspring can be only partly rescued by fostering them with normal dams beginning on postnatal day 1, implicating the perinatal period as a critical developmental window [20].

Gut microbiome can not only be associated with gastrointestinal and chronic diseases but there is also a strong connection between gut microbial diversity and psychiatric disorders. The important factors including stress, role of pre, pro-biotics and bidirectional communication as “microbiome-gut axis”. The microbiota alterations and their results in the development of psychiatric disorders, including major depressive disorder, schizophrenia (SCZ), bipolar disorder (BD), and autism spectrum disorder (ASD) [21]. Depression is described as a common mental disorder; a person in depression takes two weeks to recover from emotional disturbance and high sadness. The patient in depression is feel alone and helpless and prohibit any social gathering. It is also a cause of highly disturbed mental disturbance and can also end up in suicide. The studies showed data about the microbiome diversity alteration in depressed patients. The data showed Alistipes genus associated with inflammation and oscillibacter in high colonies with valeric acid production in depression patients [22]. Zhang et al showed, using a mouse model, that microbiota dysbiosis was associated with greater intestinal permeability and systemic inflammation. As a result of endogenous melatonin reduction (EMR), the composition of the mice microbiota changed and consisted of a decrease in the relative abundance of Bacteroidetes, an alteration of the Firmicutes/Bacteroidetes ratio, and growth of the relative abundance of Lactobacillus. The study also revealed improved gut permeability (leaky gut) and systemic inflammation in EMR mice [23].

Bipolar disorder is similar to schizophrenia and cause episodes of depression attack, inflammation. The studies have been conducted on intestinal microbiome diversity, high amount of Coriobacteriaceae was directly linked with an increased cholesterol level and high amount of Lactobacilli contributes to the development of obesity associated with Bipolar Disorder [21]. The low amount of Faecalibacterium, an autochthonous intestinal bacterium, can also be correlated with bipolar disorder. In patients diagnosed with BD, the number of Clostridiaceae involved in the fermentation of carbohydrates leading to the production of Short Chain Fatty Acids was four times lower than in the control group lead to obesity [24]. Recent studies have highlighted the crucial role of the gut microbiome, and its disruption, on the gut-brain axis in psychopathologies which includes schizophrenia (SCZ) and autism [25]. Association studies of microbiome and SCZ have been carried out on US, Chinese and European subjects. Such studies have provided evidence that gut microbiome in SCZ patients is indeed different from the normal healthy subjects. There is much interest in how the gut microbiome impacts the health of individuals. The diversity of microbiota varies from person to person and is also dependent on environmental factors. Besides bacteria, the gut microbiome also includes archaea, viruses, fungi, and protozoa. Microbiota shaping is influenced by various environmental factors such as living arrangements, smoking, depression, and also location [26]. Alteration of gut microbiota-dysbiosis drives different disease conditions from neurodevelopment and neuropsychiatric disorder to chronic distress. Microbiome modulators, prebiotics,

are designed with the aim to correct dysbiosis, depending on the type, stage, and severity of the disease, and restoring its function [27].

The advancements in sequencing technology with characterization and probing of SCZ gut microbiome have the potential to provide valuable clues for the diagnosis and prognosis of SCZ. Given the different culture, diet and conditions of the Pakistani population, this exercise is likely to generate data that could be used for further studies [28].

Risk factors for schizopherenia and association with the gut microbiota: Schizophrenia is a complex and debilitating mental disorder that affects approximately 1% of the global population. Despite extensive research, the underlying causes of schizophrenia are still not fully understood. However, there is growing evidence to suggest that the gut microbiota, the collection of microorganisms that live in the human gut, may play a role in the development of this disorder. There are several risk factors for the development of schizophrenia, including genetic predisposition, prenatal and perinatal complications, and exposure to environmental toxins. Studies have found that individuals with a family history of schizophrenia are more likely to develop the disorder, suggesting that genetic factors play a role. Additionally, exposure to certain toxins, such as lead and polychlorinated biphenyls (PCBs), during prenatal and perinatal periods may increase the risk of developing schizophrenia later in life [29].

Recent research has also suggested that the gut microbiota may be associated with the development of schizophrenia. The gut microbiome is known to play a key role in maintaining overall health, including the regulation of the immune system, the metabolism of nutrients, and the production of neuroactive compounds. Studies have found that individuals with schizophrenia have a distinct gut microbiome compared to healthy individuals, characterized by a reduced diversity of gut bacteria and an increased presence of certain types of bacteria, such as Clostridium and Lactobacillus [30].

One theory is that the gut microbiome may play a role in the development of schizophrenia through its impact on the immune system. The gut microbiome is known to play a key role in the regulation of the immune system, and imbalances in the gut microbiome have been linked to the development of immune-mediated disorders. Studies have found that individuals with schizophrenia have an overactive immune system and increased levels of inflammation, which may contribute to the development of the disorder. Another theory is that the gut microbiome may affect the production of neuroactive compounds, such as serotonin and dopamine, which play a key role in regulating mood and behavior. Studies have found that individuals with schizophrenia have alterations in the levels of these compounds, which may contribute to the development of the disorder. The gut microbiome is known to play a key role in the metabolism of certain nutrients, such as tryptophan, which is a precursor to serotonin. Imbalances in the gut microbiome may affect the metabolism of tryptophan, leading to alterations in serotonin levels.

The gut-brain axis is a complex communication system between the gut and the brain, which is mediated by the gut microbiome. The gut microbiome is capable of producing a wide range of compounds, including neurotransmitters, hormones, and immune modulators, that can affect the brain (Table 1). The gut microbiome may affect the brain by altering the levels of these compounds, or by activating immune system response, which leads to inflammation, which affects the brain function [31].

While the underlying causes of schizophrenia are still not fully understood, there is growing evidence to suggest that the gut microbiome may play a role in the development of this disorder. The gut microbiome is known to play a key role in maintaining overall health and is capable of producing a wide range of compounds that can affect the brain. Studies have found that individuals with schizophrenia have a distinct gut microbiome characterized by a reduced diversity of gut bacteria and an increased presence of certain types of bacteria, such as Clostridium and Lactobacillus. Further research is needed to fully understand the relationship between the gut microbiome and schizophrenia, but this growing body of evidence suggests that the gut microbiome may be a promising target for the development of new treatments for this debilitating disorder [32].

Microbiota and Immune cell interaction with gut microbiome in schizopherenia: The gut microbiota diversity plays a critical role in the development of the neuroimmune system, which includes myelination, neuronal remodeling and synaptic pruning. This signaling is of great important during early development post natal development stages; it's also an important determinant of cognitive function and emotional behavior. The interaction between gut microbiome immune cells and brain has led to the discovery of unknown interactions which not only includes the maintenance of lipids and glucose homestasis. It is recently discovered that the gram negative bacteria present in gut and representing as the main bacterial colonization that triggered the synthesis of LPS which directly interact with innate immune system. The production of LPS in gut can also trigger the low grade inflammation and insulin resistance lead to metabolic endotoxaemia disease. This disease is highly associated with metabolism dysbiosis of LPS causing obesity by altering the metabolic pathway. Previously studies indicated that gut microbes are directly deal with epithelial cells and translocate bacterial components in to human body [33]. Gut barrier must be highly efficient to deal with translocation of components. The gut barrier is controlled by highly efficient communications occurring between gut microbes and the host immune system. Immune cells intolerance is associated with bowel inflammation and increase the chance of diabetes 2 [34]. The complexity of these gut microbiome interactions raises the question about the level of current understanding and eventually contributes to explain why it is relatively difficult to develop specific therapeutic targets [35]. The variation in host gut microbiome can trigger different responses and it is very difficult to find out and locate this alteration in interaction with immune cells. This study is limited till now due to the complexity of variation in immune cells interaction with host gut barriers [36]. The study of rodents shows changes in behaviors and social interactions such as autism and schizopherenia. Addition of bacteriodes fragilis was considered beneficial to overcome anxiety, controlled behavior and corrected the overall gut permeability. In recent fecal microbiota transplantation (FMT) study, GF mice colonized with human autism and schizophrenia microbiota displayed alternative splicing of autism relevant genes, social and repetitive behavioral abnormalities and altered metabolome profiles compared to GF mice transplanted with fecal samples from typically developing. Furthermore, production of microbial metabolites like taurine and the fermentation product of proline - both GABA-A receptor agonists) to a BTBR autism mouse model, improved the ASD-like behaviors. Taken together, these pre-clinical studies suggest that microbial-based strategies may show promise in ameliorating social dysfunction, characteristic of both autism and schizophrenia [37].

Gut Microbiota and microglia in development and adversity of schizopherenia: One theory is that the altered gut microbiota in individuals with schizophrenia may contribute to the development of the disorder by altering the immune system and neurodevelopment. The gut microbiota is known to play a role in the production of neurotransmitters such as serotonin and dopamine, which are important for mood regulation. Additionally, the gut microbiota also plays a role in the production of inflammatory molecules such as cytokines, which may contribute to inflammation and neurodegeneration in schizophrenia [38].

Recent studies have highlighted the potential role of microglia and gut microbiota in the development of schizophrenia. Microglia, the resident immune cells of the central nervous system, play a crucial role in maintaining brain health and have been found to be activated in individuals with schizophrenia, potentially contributing to neuroinflammation and neurodegeneration. The gut-microbiota-brain axis, a complex communication pathway

connecting the gut and the brain, has been found to be disrupted in individuals with schizophrenia, potentially leading to changes in neurotransmitters and inflammatory molecules. Studies suggest that this disruption may be caused by altered gut microbiota in individuals with schizophrenia, which can produce inflammatory molecules such as cytokines, activating microglia and impacting the activity of the vagus nerve, which connects the gut and the brain. While more research is needed to fully understand the exact mechanisms by which the gut microbiota and microglia contribute to the disorder and to develop new treatments targeting these systems, these findings suggest the importance of considering the gut-brain axis in the management of schizophrenia [39].

Stress and depression are common comorbidities in individuals with schizophrenia, and the role of the microbiome in these conditions has been the subject of recent research. The microbiome refers to the collection of microorganisms that inhabit the human body, with a particular focus on the gut microbiota.Studies have found that the gut microbiota is altered in individuals with schizophrenia, with decreased diversity and changes in the relative abundance of certain bacterial species. These changes in the gut microbiota have been associated with alterations in immune function and neurotransmitter production, which may contribute to the development of stress and depression in individuals with schizophrenia [40]. One theory is that the altered gut microbiota in individuals with schizophrenia may lead to increased inflammation, which has been linked to the development of stress and depression (Table 2). Inflammatory molecules such as cytokines, produced by the gut microbiota, can impact the brain function and lead to changes in neurotransmitters such as serotonin and dopamine, which are important for mood regulation. Recent studies have also found that the gut-microbiota-brain axis, which connects the gut and the brain, is mediated by the vagus nerve. The gut microbiota can influence the activity of the vagus nerve and impact the brain function, which could be involved in the development of stress and depression in individuals with schizophrenia. Additionally, changes in the gut microbiome have been associated with changes in the gut-blood barrier integrity and an increase in permeability, which can lead to the leakage of bacterial products into the bloodstream and contribute to the systemic inflammation, which is a well-known risk factor for stress and depression [41].

The gut microbiome plays a potential role in the development of stress and depression in individuals with schizophrenia. Further research is needed to understand the exact mechanisms by which the gut microbiome contributes to these comorbidities and to develop new treatments that target the gut microbiome in individuals with schizophrenia. However, it is important to note that stress and depression are complex conditions that involve multiple interacting factors, and more research is needed to fully understand the role of the gut microbiome in these conditions in individuals with schizophrenia [42].

Gut microbial Serotonin (5-HT) and kynurenine production pathways during schizopherenia patients: Serotonin (5-HT) and kynurenine are important molecules involved in the development of schizophrenia. Recent research has focused on the role of the gut microbiome in the production of these molecules in individuals with schizophrenia. Serotonin is a neurotransmitter that plays a crucial role in mood regulation and the gut microbiome is known to produce up to 95% of serotonin in the body [43]. Studies have shown that individuals with schizophrenia have altered gut microbiome with decreased levels of beneficial bacteria such as Bifidobacterium and Lactobacillus, which are known to produce serotonin. This alteration in gut microbiome leads to the decrease in serotonin levels which may contribute to the development of schizophrenia. Kynurenine is an intermediate molecule in the tryptophan metabolism pathway, which is also involved in the development of schizophrenia. Recent studies have shown that the gut microbiome can modulate the kynurenine pathway by producing enzymes that metabolize tryptophan into kynurenine. The gut microbiome of individuals with schizophrenia has been found to have an altered kynurenine pathway, which may contribute to the development of the disorder [44].

Additionally, it is worth mentioning that the gut-microbiota-brain axis is mediated by the vagus nerve, which connects the gut and the brain. The gut microbiome can influence the activity of the vagus nerve and impact the brain function, which could be involved in the development of schizophrenia. Also, the gut microbiome can influence the host's immune system, which can lead to an increase in inflammation, which is a well-known risk factor for the development of schizophrenia [45].

The gut microbiome plays a potential role in the production of serotonin and kynurenine in individuals with schizophrenia. Further research is needed to understand the exact mechanisms by which the gut microbiome contributes to the production of these molecules and how it is related to the development of schizophrenia. However, it is important to note that schizophrenia is a complex disorder with multiple interacting factors and more research is needed to fully understand the role of the gut microbiome in the production of serotonin and kynurenine in individuals with schizophrenia [46].

Short chain fatty acids (SCFAs) are a group of fatty acids that are produced by the gut microbiota through the fermentation of dietary fibers. These molecules play an important role in maintaining gut health and have been linked to various physiological processes including energy metabolism, immune function, and brain function. Recent studies have shown that the gut microbiota is altered in individuals with schizophrenia, with changes in the relative abundance of certain bacterial species that are involved in SCFA production [47]. These changes in the gut microbiota may lead to alterations in SCFA production and contribute to the development and adversity of schizophrenia. For example, SCFA such as butyrate produced by the gut microbiota is known to have anti-inflammatory properties, and a decrease in butyrate production due to altered gut microbiota might contribute to the inflammation and neurodegeneration seen in schizophrenia. Additionally, SCFA such as acetate, propionate and butyrate can cross the blood-brain barrier and modulate the activity of the brain-derived neurotrophic factor (BDNF) which is involved in the neuroplasticity and the development of schizophrenia Figure 1 [48].

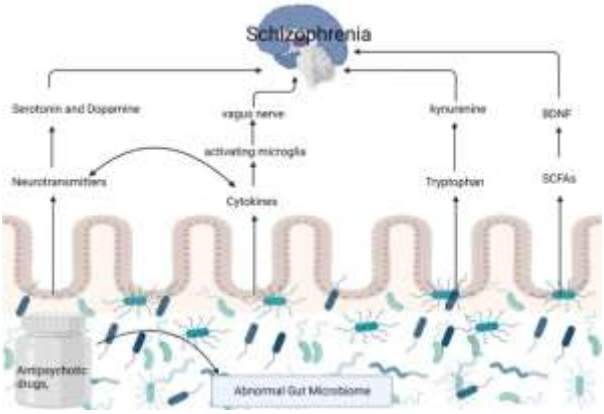

Figure 1: Illustration of different metabolites production in SCZ patients and their gut

Clinical schizophrenia studies and gut microbiota diversity variation: Clinical studies on schizophrenia (SCZ) and gut microbiota diversity have provided insights into the potential role of the gut microbiome in the etiology and pathogenesis of this psychiatric disorder. The gut microbiome, which includes bacteria, archaea, viruses, fungi, and protozoa, plays a critical role in regulating multiple physiological processes, including immune function, metabolism, and brain development. Alterations in gut microbiota, also known as dysbiosis, have been linked to various disease conditions, including neurodevelopment and

neuropsychiatric disorders. Several studies have reported differences in gut microbiome diversity between individuals with SCZ and healthy controls. A study by Li et al. (2018) found that individuals with SCZ had lower levels of bacterial diversity and increased levels of Lactobacillus and Streptococcus compared to healthy controls. Another study by Severance et al. (2016) reported an increase in the relative abundance of the genus Coprococcus and a decrease in the relative abundance of the genus Faecalibacterium in individuals with SCZ. These findings suggest that alterations in the gut microbiome may play a role in the development of SCZ [49].

The gut-brain axis, which refers to the communication between the gut and the brain, has been proposed as a potential mechanism by which gut microbiota may influence the development of SCZ. The gut microbiome produces various neurotransmitters, including dopamine and serotonin, which are involved in regulating mood and cognitive function. Dysregulation of these neurotransmitters has been implicated in the pathogenesis of SCZ. Additionally, the gut microbiome plays a critical role in regulating the immune system, and alterations in gut microbiota have been linked to inflammation, which has been associated with SCZ. Prebiotics, probiotics, and symbiotic have been proposed as potential therapies for SCZ based on their ability to modulate gut microbiome diversity and function. Prebiotics are non-digestible carbohydrates that stimulate the growth of beneficial bacteria in the gut. Probiotics are live microorganisms that, when consumed in adequate amounts, provide health benefits [50].

Antipsychotic drugs, which are commonly used to treat schizophrenia and other psychiatric disorders, have been shown to have a significant impact on the gut microbiome. Studies have found that patients with schizophrenia who take antipsychotic drugs have a different composition of gut bacteria compared to those who do not take the drugs. Specifically, research has revealed that antipsychotic drugs can alter the abundance of certain bacterial groups, such as Bacteroidetes and Firmicutes, in the gut microbiome of patients with schizophrenia. Additionally, antipsychotic drugs have been found to reduce the overall diversity of the gut microbiome, which may contribute to the development of gut-related side effects such as constipation, diarrhea, and weight gain. The exact mechanisms by which antipsychotic drugs affect the gut microbiome are not yet fully understood, but it is thought that the drugs may alter gut motility, change the availability of nutrients for bacterial growth, or modulate the immune system, which in turn could affect the gut microbiome [51].

Overall, the research highlights the importance of understanding the interplay between antipsychotic drugs and the gut microbiome in patients with schizophrenia. Further studies are needed to determine the long-term effects of antipsychotic drugs on the gut microbiome and to identify potential strategies for mitigating any negative effects. It is also important to note that, while antipsychotic drugs play an important role in treating schizophrenia, they are not without their side effects, and alternative treatments such as talk therapy or dietary interventions should also be considered.

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, the gut microbiome plays a crucial role in the development of neurological disorders such as schizophrenia. Studies have shown that the gut microbiome is altered in individuals with schizophrenia and these changes may contribute to the development of the disorder. For example, studies have found that individuals with schizophrenia have lower levels of certain beneficial bacteria, such as Bifidobacterium and Lactobacillus, and higher levels of potentially harmful bacteria, such as Proteobacteria. Additionally, research has also revealed that the gut-brain axis, which is the communication between the gut and the brain, is disrupted in individuals with schizophrenia. While more research is needed to fully understand the relationship between the gut microbiome and schizophrenia, current findings suggest that targeting the gut microbiome may be a potential therapeutic approach for individuals with the disorder. For example, probiotics, which are live microorganisms that are similar to the beneficial bacteria found in the gut, have been shown to improve symptoms of schizophrenia in some studies. Additionally, dietary interventions, such as the Mediterranean diet, which is high in fruits, vegetables, and fish, have also been found to improve gut microbiome diversity and may be beneficial for individuals with schizophrenia.

In the future, more research is needed to fully understand the complex interactions between the gut microbiome and schizophrenia, including the mechanisms by which the gut microbiome may contribute to the development of the disorder. This research will be essential for the development of targeted therapies for individuals with schizophrenia and for a better understanding of the role of the gut microbiome in mental health more broadly. Additionally, it's important to note that this is only one aspect of Schizophrenia, as the disorder is multifactorial, and more research is needed to understand the other contributing factors.

Acknowledgement and Funding: We are thankful to University of Management and Technology, Lahore, Pakistan for providing suitable environment to conduct this review. This work is funded by International Foundation for Science (IFS) under Grantee: I-1-C-6501-1 to Mr. Athar Hussain.

Ethics approval and consent to participate: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

REFERENCES

1. Kim, M. H., Yun, K. E., Kim, J., Park, E., Chang, Y., Ryu, S and Kim, H. N. (2020). Gut microbiota and metabolic health among overweight and obese individuals. Scientific reports, 10(1), 1-11.
2. Umair, S. Z., Ashfaq, M., Farooq, R., Farid, G., & Iqbal, R. S. (2022). Impact and Burden on the Quality of Life of Primary Caregivers of Schizophrenic Patients Presented in Lahore General Hospital. Pakistan Journal of Medical & Health Sciences, 16(10), 652-652.
3. Zhang, S., Zeng, B., Chen, Y., Yang, M., Kong, F., Wei, L and Li, Y. (2021). Gut microbiota in healthy and unhealthy long-living people. Gene, 779, 145510.
4. Cataldi, S., Bonavolontà, V., Poli, L., Clemente, F. M., De Candia, M., Carvutto, R and Fischetti, F. (2022). The Relationship between Physical Activity, Physical Exercise, and Human Gut Microbiota in Healthy and Unhealthy Subjects: A Systematic Review. Biology, 11(3), 479.
5. Cataldi, S., Bonavolontà, V., Poli, L., Clemente, F. M., De Candia, M., Carvutto, R and Fischetti, F. (2022). The Relationship between Physical Activity, Physical Exercise, and Human Gut Microbiota in Healthy and Unhealthy Subjects: A Systematic Review. Biology, 11(3), 479.
6. Olivares, P. D. S. G., Pacheco, A. B. F., Aranha, L. N., da Silva Oliveira, B., Santos, A. A., Dos Santos, P. C. M and Oliveira, G. M. M. (2021). Gut microbiota of adults with different metabolic phenotypes. Nutrition, 90, 111293.
7. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). European psychiatry. 2009 Sep;24(6):412-24.
8. McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, Aksenov AA, Behsaz B, Brennan C, Chen Y, DeRight Goldasich L. American gut: an open platform for citizen science microbiome research. Msystems. 2018 May 15;3(3):e00031-18.
9. Asnicar, F., Berry, S. E., Valdes, A. M., Nguyen, L. H., Piccinno, G., Drew, D. A. and Segata, N. (2021). Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. Nature Medicine, 27(2), 321-332.
10. Schwarz E, Maukonen J, Hyytiäinen T, Kieseppä T, Orešič M, Sabunciyan S, Mantere O, Saarela M, Yolken R, Suvisaari J. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. Schizophrenia research. 2018 Feb 1;192:398-403.

11. Tomlinson J, Medlinskiene K, Cheong VL, Khan S, Fylan B. Patient and public involvement in designing and conducting doctoral research: the whys and the hows. Research Involvement and Engagement. 2019 Dec;5(1):1-2.
12. Nguyen TT, Kosciolek T, Maldonado Y, Daly RE, Martin AS, McDonald D, Knight R, Jeste DV. Differences in gut microbiome composition between persons with chronic schizophrenia and healthy comparison subjects. Schizophrenia research. 2019 Feb 1;204:23-9.
13. Zhu F, Ju Y, Wang W, Wang Q, Guo R, Ma Q, Sun Q, Fan Y, Xie Y, Yang Z, Jie Z. Metagenome-wide association of gut microbiome features for schizophrenia. Nature communications. 2020 Mar 31;11(1):1-0.
14. Li S, Song J, Ke P, Kong L, Lei B, Zhou J, Huang Y, Li H, Li G, Chen J, Li X. The gut microbiome is associated with brain structure and function in schizophrenia. Scientific reports. 2021 May 7;11(1):1-1.
15. Nguyen TT, Kosciolek T, Maldonado Y, Daly RE, Martin AS, McDonald D, Knight R, Jeste DV. Differences in gut microbiome composition between persons with chronic schizophrenia and healthy comparison subjects. Schizophrenia research. 2019 Feb 1;204:23-9.
16. Shen Y, Xu J, Li Z, Huang Y, Yuan Y, Wang J, Zhang M, Hu S, Liang Y. Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: a cross-sectional study. Schizophrenia research. 2018 Jul 1;197:470-7.
17. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). European psychiatry. 2009 Sep;24(6):412-24.
18. Xu, H., Liu, M., Cao, J., Li, X., Fan, D., Xia, Y., ... & Zhao, H. (2019). The dynamic interplay between the gut microbiota and autoimmune diseases. Journal of immunology research, 2019.
19. Lee, J. E., Walton, D., O'Connor, C. P., Wammes, M., Burton, J. P., & Osuch, E. A. (2022). Drugs, guts, brains, but not rock and roll: The need to consider the role of gut microbiota in contemporary mental health and wellness of emerging adults. International Journal of Molecular Sciences, 23(12), 6643.
20. Vangoitsenhoven, R., & Cresci, G. A. (2020). Role of microbiome and antibiotics in autoimmune diseases. Nutrition in Clinical Practice, 35(3), 406-416.
21. Khan, M. F., & Wang, H. (2020). Environmental exposures and autoimmune diseases: contribution of gut microbiome. Frontiers in immunology, 3094.
22. Opazo, M. C., Ortega-Rocha, E. M., Coronado-Arrázola, I., Bonifaz, L. C., Boudin, H., Neunlist, M., ... & Riedel, C. A. (2018). Intestinal microbiota influences non-intestinal related autoimmune diseases. Frontiers in microbiology, 9, 432.
23. Liu, G., Yu, Q., Tan, B., Ke, X., Zhang, C., Li, H., ... & Lu, Y. (2022). Gut dysbiosis impairs hippocampal plasticity and behaviors by remodeling serum metabolome. Gut Microbes, 14(1), 2104089.
24. Hrncir, T. (2022). Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options. Microorganisms, 10(3), 578.
25. Vijay, A., & Valdes, A. M. (2022). Role of the gut microbiome in chronic diseases: A narrative review. European Journal of Clinical Nutrition, 76(4), 489-501.
26. Lecomte, V., Kaakoush, N. O., Maloney, C. A., Raipuria, M., Huinao, K. D., Mitchell, H. M., & Morris, M. J. (2015). Changes in gut microbiota in rats fed a high fat diet correlate with obesity-associated metabolic parameters. PloS one, 10(5), e0126931.
27. Cresci, G. A., & Bawden, E. (2015). Gut microbiome: what we do and don't know. Nutrition in Clinical Practice, 30(6), 734-746.
28. Davenport, E. R., Mizrahi-Man, O., Michelini, K., Barreiro, L. B., Ober, C., & Gilad, Y. (2014). Seasonal variation in human gut microbiome composition. PloS one, 9(3), e90731.
29. Davenport, E. R., Mizrahi-Man, O., Michelini, K., Barreiro, L. B., Ober, C., & Gilad, Y. (2014). Seasonal variation in human gut microbiome composition. PloS one, 9(3), e90731.
30. Hall, A. B., Tolonen, A. C., & Xavier, R. J. (2017). Human genetic variation and the gut microbiome in disease. Nature Reviews Genetics, 18(11), 690-699.
31. Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., ... & Bork, P. (2011). Enterotypes of the human gut microbiome. nature, 473(7346), 174-180.
32. Shaheen, W. A., Quraishi, M. N., & Iqbal, T. H. (2022). Gut microbiome and autoimmune disorders. Clinical and Experimental Immunology.
33. Carbia, C., Lannoy, S., Maurage, P., López-Caneda, E., O'Riordan, K. J., Dinan, T. G., and Cryan, J. F. (2021). A biological framework for emotional dysregulation in alcohol misuse: from gut to brain. Molecular Psychiatry, 26(4), 1098-1118.
34. Daily, J. W., and Park, S. (2022). Sarcopenia is a cause and consequence of metabolic dysregulation in aging humans: Effects of gut dysbiosis, glucose dysregulation, diet and lifestyle. Cells, 11(3), 338.
35. Belizário, J. E., Faintuch, J., and Garay-Malpartida, M. (2018). Gut microbiome dysbiosis and immunometabolism: new frontiers for treatment of metabolic diseases. Mediators of Inflammation, 2018.
36. Daily, J. W., and Park, S. (2022). Sarcopenia is a cause and consequence of metabolic dysregulation in aging humans: Effects of gut dysbiosis, glucose dysregulation, diet and lifestyle. Cells, 11(3), 338.
37. Cheng, M., Zhao, Y., Cui, Y., Zhong, C., Zha, Y., Li, S. and Han, J. (2022). Stage-specific roles of microbial dysbiosis and metabolic disorders in rheumatoid arthritis. Annals of the Rheumatic Diseases, 81(12), 1669-1677.
38. Zhao, M., Zhang, J., Liu, T., Wang, J., Cai, H., Zhang, X., and Tang, J. (2022). Differential modulations of lauric acid and its glycerides on High fat diet-induced metabolic disorders and gut microbiota dysbiosis. Food Research International, 111437.
39. Li, D., Li, Y., Yang, S., Lu, J., Jin, X., and Wu, M. (2022). Diet-gut microbiota-epigenetics in metabolic diseases: From mechanisms to therapeutics. Biomedicine & Pharmacotherapy, 153, 113290.
40. David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., ... & Turnbaugh, P. J. (2014). Diet rapidly and reproducibly alters the human gut microbiome. Nature, 505(7484), 559-563.
41. Browne, H. P., Forster, S. C., Anonye, B. O., Kumar, N., Neville, B. A., Stares, M. D., ... & Lawley, T. D. (2016). Culturing of 'unculturable'human microbiota reveals novel taxa and extensive sporulation. Nature, 533(7604), 543-546.
42. Lloyd-Price, J., Mahurkar, A., Rahnavard, G., Crabtree, J., Orvis, J., Hall, A. B., ... & Huttenhower, C. (2017). Strains, functions and dynamics in the expanded Human Microbiome Project. Nature, 550(7674), 61-66.
43. Ross, B. D., Verster, A. J., Radey, M. C., Schmidtke, D. T., Pope, C. E., Hoffman, L. R., ... & Mougous, J. D. (2019). Human gut bacteria contain acquired interbacterial defence systems. Nature, 575(7781), 224-228.
44. Fluhr, L., Mor, U., Kolodziejczyk, A. A., Dori-Bachash, M., Leshem, A., Itav, S., ... & Elinav, E. (2021). Gut microbiota modulates weight gain in mice after discontinued smoke exposure. Nature, 600(7890), 713-719.
45. Gacesa, R., Kurilshikov, A., Vich Vila, A., Sinha, T., Klaassen, M. A. Y., Bolte, L. A., ... & Weersma, R. K. (2022). Environmental factors shaping the gut microbiome in a Dutch population. Nature, 604(7907), 732-739.
46. Zhang, Y., Bhosle, A., Bae, S., McIver, L. J., Pishchany, G., Accorsi, E. K., ... & Franzosa, E. A. (2022). Discovery of bioactive microbial gene products in inflammatory bowel disease. Nature, 1-7.
47. Wu, J., Gan, T., Zhang, Y., Xia, G., Deng, S., Lv, X., ... & Lv, B. (2020). The prophylactic effects of BIFICO on the antibiotic-induced gut dysbiosis and gut microbiota. Gut Pathogens, 12(1), 1-11.
48. Gobbo, M. M., Bomfim, M. B., Alves, W. Y., Oliveira, K. C., Corsetti, P. P., & de Almeida, L. A. (2022). Antibiotic-induced gut dysbiosis and autoimmune disease: A systematic review of preclinical studies. Autoimmunity Reviews, 103140.
49. Duan, H., Yu, L., Tian, F., Zhai, Q., Fan, L., & Chen, W. (2022). Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies. Critical reviews in food science and nutrition, 62(6), 1427-1452.
50. Siddiqui, R., Mungroo, M. R., Alharbi, A. M., Alfahemi, H., & Khan, N. A. (2022). The Use of Gut Microbial Modulation Strategies as Interventional Strategies for Ageing. Microorganisms, 10(9), 1869.
51. Yang, L., Bajinka, O., Jarju, P. O., Tan, Y., Taal, A. M., & Ozdemir, G. (2021). The varying effects of antibiotics on gut microbiota. AMB Express, 11(1), 1-13.
52. Kelly, J. R., Minuto, C., Cryan, J. F., Clarke, G., & Dinan, T. G. (2021). The role of the gut microbiome in the development of schizophrenia. Schizophrenia Research, 234, 4-23.