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Authors' Affiliation:
[1]Medical University of Łódź al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland
[2]University of Warmia and Mazury, Michała Oczapowskiego 2, Olsztyn, Poland
[3]Wrocław Medical University wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland
[4]Medical University in Lublin Al. Racławickie 1, 20-059 Lublin, Poland

***Corresponding author:**
Witold Czarnik
Medical University of Łódź al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland; phone number: +48 737 169 017

Orcid and contact list:

Witold Czarnik	0009-0002-5502-0335, witoldczarnik1@gmail.com
Anna Broniecka	0009-0000-9900-8093, anna.broniecka@stud.umed.lodz.pl
Karol Batko	0009-0000-9949-508X, karol.batko@stud.umed.lodz.pl
Aleksandra Jakubczak	0009-0004-6765-3257, aleksandra.jakubczak@stud.umed.lodz.pl
Stanisław Malik	0009-0006-5634-308X, stanislaw.malik@stud.umed.lodz.pl
Katarzyna Wacławek	0009-0002-0612-7451, Waclawekatarzyna@gmail.com
Klaudia Głodowska	0009-0007-4389-0591, klaudia.glodowska@student.umw.edu.pl
Małgorzata Bacik	0009-0006-8350-5064, malgorzata.bacik@student.umw.edu.pl
Bartłomiej Józef Rdzanek	0009-0003-2629-6081, Bartlomiej.Rdz@gmail.com

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Dietary and gut microbial factors in the development of bipolar disorder

Witold Czarnik[1*], Anna Broniecka[1], Karol Batko[1], Aleksandra Jakubczak[1], Stanisław Malik[1], Katarzyna Wacławek[2], Klaudia Głodowska[3], Małgorzata Bacik[3], Bartłomiej Józef Rdzanek[4]

ABSTRACT

Recent scientific studies have proven that gut microbiota functions as a critical factor in mental disorder development, including bipolar disorder (BD), Depression, and Schizophrenia. The gastrointestinal tract contains microorganisms that influence neurotransmission and control neuroendocrine and immune system responses and create microbial metabolites to manage inflammation. The management of psychiatric conditions shows promise through microbiota-directed interventions which include dietary changes probiotics and fecal microbiota transplantation (FMT). The current review examines existing studies about how gut microbiota, together with dietary components, influence bipolar disorder progression from its first stages until its full development.

keywords: gut microbiota, bipolar disorder, Mediterranean diet

1. INTRODUCTION

Bipolar Disorder (BD) presents as a mental health condition that causes people to experience alternating cycles of depression and elevated mood states that include mania or hypomania and sometimes mixed emotional episodes (Nierenberg et al., 2023). The disorder shows no symptoms between episodes when patients experience remission periods. Each phase of BD can be accompanied by psychotic symptoms, most often delusions that align with the mood prevailing at the time. For most patients, depressive states predominate, accounting for up to 70% of the duration of the illness (Smith et al., 2012).

BD is the 17th leading cause of the global burden of disease, following depression, anxiety disorders, schizophrenia, and dysthymia. BD affects more than 1% of the world's population. The estimated lifetime prevalence of BD type I is 0.6%, and for type II, it is 0.4%, with type II more commonly affecting women (Vieta et al., 2018). The onset of BD typically occurs between the ages of 20 and 30. An earlier onset is associated with a higher number of comorbidities and usually begins with a depressive episode. BD is one of the significant causes of disability in young people, as it can lead to cognitive impairments. The age group faces elevated

mortality rates because of suicides and cardiovascular diseases, according to Vieta et al., (2018). The suicide risk among BD patients reaches 6-7% while their death rates from suicide exceed general population numbers by 20 to 30 times (McGuinness et al., 2022). The patient population shows multiple disorders, which include anxiety in 71% of cases and substance abuse in 56%, personality disorders in 36% and ADHD in 10-20%. Research during past times linked mood disorders in BD to monoamine neurotransmitter system imbalances between serotonergic, noradrenergic, and dopaminergic pathways. Modern studies investigate how synaptic and neural plasticity mechanisms in the prefrontal cortex, hippocampus, amygdala, and limbic system areas function in BD development. The gut-brain axis plays a potential role in disorder development because changes in gut microbiota quantity or quality activate the immune system, inflammation, and create membrane permeability changes and oxidative stress (McGuinness et al., 2022).

BD has a complex genetic background, and its genesis is multifactorial: genetic factors, such as standard and rare variants, and environmental factors contribute to its development. The heritability of BD is very high, ranging from 70 to 90%. Although bipolar affective disorders are among the most heritable psychiatric disorders, environmental factors also contribute to the development of the disease, and its etiology is best explained by a model considering gene-environment interactions. Epigenetic changes may mediate these interactions (Post, 2016). Environmental factors increasing the risk of BD include perinatal risk factors such as cesarean delivery, maternal influenza infection during pregnancy, maternal smoking during pregnancy, and older paternal age (Vieta et al., 2018). Adverse life events, especially traumatic childhood experiences, have been classically described as risk factors for BD. Substance abuse plays the same role - cannabis or other drug use by adolescents can lead to early onset of BD and cause a more severe course (Vieta et al., 2018).

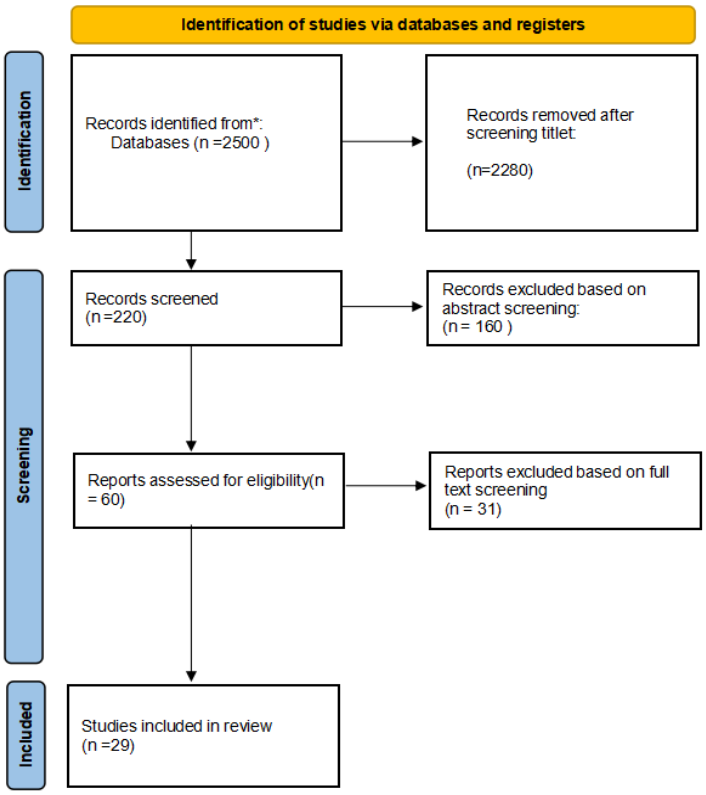

Figure 1: The PRISMA flow diagram shows the process of study identification and screening.

2. REVIEW METHODS

The authors searched PubMed, Scopus, and Google Scholar databases using phrases that contain keywords like "bipolar disease", "gut microbiota", "Mediterranean diet", and "gut-brain axis". We selected studies by title, abstract, and based on their availability. Boolean operators such as “AND” and “OR” were applied to refine and optimize the search results. The final number of studies included in our review is 29. We included only articles written in English from 2005 to 2023. The article screening process adhered to the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

3.1. Gut Microbiota

The human digestive tract contains diverse microbial populations of microorganisms that operate as an anaerobic bioreactor. The Microbiota includes bacteria, viruses, yeasts, archaea, protozoa and parasites but bacteria make up the majority of its components. Research by Cryan et al., (2019) shows that bacterial cells in human intestines number more than 100 trillion. The gut contains the majority of human microorganisms, which include more than 1500 bacterial species that have a combined gene count exceeding 150 times the amount of human DNA (Qin et al., 2010). The human microbiome contains two main bacterial groups, which were identified by Eckburg et al., (2005) as Firmicutes and Bacteroidetes.

The gastrointestinal tract receives its first bacterial colonizers at birth when newborns meet maternal microbiota and environmental substances. The development of gut Microbiota occurs through exposure to maternal Microbiota and ecological factors, as suggested by the studies (Perez-Muñoz et al., 2017). The two main elements that influence this process are delivery approach (cesarean section or natural birth) and infant nutrition method (breast milk or formula) (Guo et al., 2023). The process depends heavily on antibiotic use as well as antibiotic-like substances (Liu et al., 2020). The digestive system reaches eubiosis or "healthy microbiota" status through the peaceful coexistence of beneficial bacteria. A person's microbiome exists in a natural state of eubiosis, but their intestinal permeability and species composition can change based on their diet and lifestyle choices. The condition of "leaky gut" occurs when the intestinal barrier weakens through the expansion of spaces between epithelial cells that line the intestine. The condition develops from unhealthy lifestyles and excessive alcohol consumption. The uncontrolled movement of bacterial species through intestinal microbiota leakage results in the release of toxic metabolites. Research shows that systemic inflammation occurs when metabolites and pro-inflammatory factors work together to increase TNF-α and IL-6 and IL-18 cytokine levels (Di Vincenzo et al., 2024). The elevation of pro-inflammatory cytokines results in blood-brain barrier damage which creates higher permeability for harmful substances that intensify central nervous system (CNS) inflammation. The microbiota-gut-brain axis describes the interactive network that connects gut bacteria to both human brain functions and gut operations. Gut bacteria interact with the body through three main methods: metabolic byproducts, endocrine system regulation, immune system regulation, and nerve signal transmission.

The production of bioactive metabolites by gut bacteria serves as a primary mechanism through which the gut microbiota communicates with the CNS. Through the modification of internal and external chemical substances, gut bacteria enable the control of both normal and pathological human body processes. The primary mechanism through which gut bacterial metabolites affect CNS functions involves their production of neurotransmitters. The metabolic activities of Bifidobacterium and Lactobacillus bacteria result in the production of acetylcholine and gamma-aminobutyric acid (GABA) (Poluektova et al., 2021).

The gut bacteria generate serotonin through a vital biological process. The human body generates most of its serotonin through gut processes which account for more than 90% of total serotonin production. The gut contains bacteria that produce dopamine and norepinephrine and serotonin through their metabolic activities including Bacillus and Morganella and Klebsiella and Serratia. The primary metabolites from bacterial fiber fermentation produce short-chain fatty acids which control blood-brain barrier permeability and promote microglial development and enhance neurotransmitter activity and serotonin production. The inflammatory processes are influenced by SCFAs because these acids control the production and migration of neutrophils and T lymphocytes and inflammatory cytokines (Swer et al., 2023).

3.2. Gut microbiota in bipolar disorder

Research on human gut microbiota has its own specificity. The human gastrointestinal tract is characterized by different conditions in its various segments, resulting in a vast diversity of microorganisms inhabiting it (Góralczyk-Bińkowska et al., 2022), some of which are non-culturable. Additionally, conducting invasive studies on humans to analyse the Microbiota in different sections of the gastrointestinal tract is complicated. Consequently, studies of Microbiota present in stool samples have gained popularity, while more invasive research methods are utilized in animal studies (Whon et al., 2021). Two primary methods of assessing stool samples are metataxonomic and metagenomic analyses. The former focuses on studying specific genes, most commonly 16S rRNA, which provides information on particular taxa.

Metagenomic analysis involves sequencing the entire DNA from the sample, offering insights into the microbiota as a functional whole, thus providing a broader view of its interactions than focusing on specific species. The methods evaluate alpha diversity, which shows the number of different taxa in one sample, and beta diversity, which shows the differences in Microbiota between different samples (McGuinness et al., 2022). The results of studies evaluating gut Microbiota in BD are inconclusive, further complicated by

fewer studies compared to other psychiatric disorders, such as depression or schizophrenia. In one meta-analysis (Nikolova et al., 2021), nine studies examining the role of microbiota in BD, involving a total of 465 patients, reported a decrease in alpha diversity among patients with BD, while no changes were noted in beta diversity.

The same study described a taxonomic composition similar across various psychiatric disorders - schizophrenia, depression, and BD. More frequent occurrences of the Eggerthella genus and Lactobacillaceae family, and less frequent occurrences of Faecalibacterium and Coprococcus genera were observed compared to the general population (Nikolova et al., 2021).

In contrast, another meta-analysis that included seven studies on BD, with a total of 527 participants, reported no changes in alpha diversity and significant differences in beta diversity among patients with BD. Additionally, a specific taxonomic composition was described in BD, similar to that seen in another affective disorder - depression (McGuinness et al., 2022). Researchers are also interested in the impact of pharmacotherapy used in BD on gut microbiota. In a study conducted on animals, an increase in alpha diversity of gut microbiota was demonstrated in rats treated with lithium, valproic acid, or aripiprazole. Increased presence of bacteria from Peptostreptococcaceae, Clostridiaceae, and Ruminococcaceae families was also observed in their gastrointestinal tracts (McGuinness et al., 2022). Another study identified changes in the taxonomic composition of gut microbiota in patients with BD after 4 weeks of quetiapine treatment compared to pre-treatment status. However, quetiapine therapy did not affect the diversity of gut microbiota.

Patients with BD often contend with numerous comorbidities, notably metabolic syndrome and obesity, affecting 37% and 21% of patients, respectively (Nierenberg et. al 2023). Numerous reports indicate an association between metabolic syndrome and changes in gut microbiota (Wang et al., 2020) in the general population, prompting analysis of gut microbiota in BD patients with elevated BMI. One study found that BD patients with concurrent overweight or obesity exhibited reduced alpha diversity compared to patients with normal weight and healthy volunteers. However, these relationships were not statistically significant.

The research study found distinct gut microbiota patterns between BD patients who maintained a normal body mass index and those who had an overweight or obese status. The Propionibacteriaceae and Sphingobacteriaceae bacterial families appeared more frequently in normal-weight patients, but the Enterococcaceae bacteria became dominant in overweight and obese patients. The control group showed higher amounts of Halomonadaceae family microorganisms according to Zhang et al., (2023).

The use of atypical antipsychotic medications (ALPP) in BD treatment may result in metabolic syndrome as an adverse side effect (Carli et al., 2021). Research has shown that metabolic syndrome produces changes in the composition of gut microbiota (Wang et al., 2020). These relationships prompt researchers to analyse whether the use of ALPP is associated with changes in gut microbiota. In one study, the diversity of gut microbiota was compared between BD patients treated with ALPP and a group of patients not taking these medications. Female patients receiving atypical ALPP had statistically significantly lower diversity of gut microbiota compared to patients treated with other medicines ($p=0.015$). This relationship was not observed in the male patient group.

The Hao et al., (2023) study on pediatric patients with psychiatric disorders who received ALPP treatment showed reduced alpha diversity in gut microbiota when compared to healthy children in the control group. The limited number of gut microbiota studies in BD requires special attention because they are fewer than the number of psychiatric disorder studies that researchers conduct in this field. The number of BD gut microbiota studies remains lower than the number of psychiatric disorder studies that focus on depression and schizophrenia. For example, one of the mentioned meta-analyses, including nine studies totalling 465 BD patients, analyzed 21 studies involving 930 patients with depression. This example, along with partially conflicting results from individual studies, illustrates the need for further exploration of gut microbiota and its role in BD (Nikolova et al., 2021).

People with BD tend to have higher rates of eating disorders than the normal population, thus developing unhealthy eating patterns and choosing unhealthy diets. People with diagnosed BD tend to consume more fat in their diet and struggle with meal planning, which may cause them to have only one meal a day. BD patients are at twice the risk of developing obesity and 1.6 times at risk of getting type 2 diabetes.

The high-fat diet (HFD) known as the Western diet consists of excessive amounts of unhealthy fats and processed foods and simple sugars and salt and other dangerous substances together with insufficient amounts of fruits and vegetables. The high-fat diet causes changes in gut microbiota composition because it increases Firmicutes and Proteobacteria and Bacteroides species but decreases Lactobacillus and Roseburia populations (Beam et al., 2021). The gut microbiome modifications lead to decreased SCFA production while generating higher amounts of inflammatory cytokines and toxic lipopolysaccharides (LPS). The body develops systemic inflammation because of elevated pro-inflammatory cytokines which then harm the blood-brain barrier to produce CNS inflammatory responses (Beam et al., 2021).

The consumption of palm oil in HFD diets causes negative effects on gut microbiota because it reduces the populations of anti-inflammatory bacteria Akkermansia muciniphila and Clostridium leptum. The high consumption of simple sugars creates an imbalance in the Firmicutes/Bacteroidetes ratio and reduces beneficial bacteria production of butyric acid (García-Montero et al., 2021).

The consumption of HFD leads to direct changes in brain dopamine and noradrenaline and serotonin activities. The reduction of hypothalamic serotonin transmission results in decreased BDNF production which supports neuron development and differentiation. The hippocampus shows decreased BDNF expression which results in poor quality of newly generated neurons. Research indicates that BDNF levels directly affect the development of mood disorders (Mansur et al., 2017). The Mediterranean diet (MD) consists of eating fruits, vegetables, fish, seafood, nuts and unsaturated fats while limiting red meat and dairy products (Zhu et al., 2023). The Mediterranean diet promotes Bacteroides bacteria growth and specific Clostridium groups that generate SCFAs while it reduces Proteobacteria and Bacillaceae phyla populations. The gut microbiota ferments dietary fiber from MD to generate SCFAs. The consumption of high dietary fiber amounts leads to reduced inflammation which decreases the chances of developing type 2 diabetes and obesity alongside BD comorbidities (García-Montero et al., 2021).

The dietary pattern of MD patients includes higher levels of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). The consumption of oleic acid as a MUFA leads to higher numbers of Bifidobacterium and Lactobacillus bacteria which produce anti-inflammatory effects. The consumption of fish and seafood and nuts containing PUFA leads to a decrease in Firmicutes/Bacteroides ratio and an increase in Lachnospiraceae and Bifidobacteria populations. The number of Enterobacteria decreases when consuming these foods because they produce toxic LPS (Ortega et al., 2023). A higher intake of seafood has also been linked with a reduced risk of BD (García-Montero et al., 2021). The research study examines how Mediterranean and Western diets affect bipolar disorder through their distinctive dietary features, which are listed in Table 1.

Table 1. Impact of Western and Mediterranean diet in relation to microbiome and BD.

Feature	**Western diet**	**Mediterranean diet**
Diet composition	Mainly saturated fatty acids, salt and sugar	Mainly unsaturated fatty acids, fish, seafoods and nuts.
Inflammation	Increased synthesis of inflammatory mediators by bacteria, generalized inflammation.	Anti-inflammatory effect, reduced risk of concomitant diseases.
Impact on microbiome	↑ Firmicutes, ↑ Proteobacteria ↓ Bacteroidetes, ↓ Lactobacillus, ↓ Roseburia, ↓ Akkermansia	↑ Bacteroidetes, ↑ Bifidobacterium, ↑ Lactobacillus, ↑ Lachnospiraceae ↓ Proteobacteria, ↓ Bacillaceae, ↓ Enterobacteria
Scfas production	Decreased	Increased

4. CONCLUSION

BD exists as a prevalent psychiatric disorder, yet scientists have not fully grasped its mechanisms. The understanding of BD etiology and treatment methods remains incomplete because these aspects directly affect the effectiveness of current therapeutic approaches. Scientists have shown rising interest in studying how gut Microbiota affects the progression of BD during recent years. The existing research findings create opportunities for scientists to conduct additional investigations. Of particular interest in the context of observed changes in gut microbiota and gut-brain axis disorders is the theory of "leaky gut" and the role of gut bacteria in the development of systemic inflammation, which may affect the functioning of the CNS in BD.

These issues are not merely theoretical considerations. There is a growing number of reports indicating the influence of diet and probiotic use on the course of BD through their impact on gut Microbiota. Recommendations for healthy eating, such as following an MD, can already be issued to patients with BD. In the future, research on gut Microbiota may provide evidence for the effectiveness of other therapies targeting the gut-brain axis, such as FMT. This could expand the repertoire of treatment options beyond conventional pharmacotherapy, potentially improving outcomes in bipolar affective disorder.

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Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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