International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	THE ROLE OF DIETARY PATTERNS AND NUTRIENTS IN SCHIZOPHRENIA: A LITERATURE REVIEW
ARTICLE INFO	Natalia Kraciuk, Alicja Bury, Karol Bartecki, Małgorzata Piekarska-Kasperska, Aleksandra Maciejczyk, Katarzyna Krupa, Julia Błoniecka, Kacper Jankowski, Anna Daniel. (2025) The Role of Dietary Patterns and Nutrients in Schizophrenia: A Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3483
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3483
RECEIVED	07 June 2025
ACCEPTED	22 July 2025
PUBLISHED	26 July 2025
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THE ROLE OF DIETARY PATTERNS AND NUTRIENTS IN SCHIZOPHRENIA: A LITERATURE REVIEW

Natalia Kraciuk *(Corresponding Author, Email: n.kraciuk@gmail.com)*
Independent Public Healthcare Establishment in Wyszkow, Al. Komisji Edukacji Narodowej 1, 07-200 Wyszków, Poland
ORCID ID: 0009-0007-8319-2296

Alicja Bury
Orlowski Hospital in Warsaw, ul. Czerniakowska 231, 00-416, Warszawa, Poland
ORCID ID: 0009-0009-2950-8741

Karol Bartecki
University Clinical Centre of the Medical University of Warsaw, Centralny Szpital Kliniczny, ul. Banacha 1a, 02-097 Warszawa, Poland
ORCID ID: 0009-0006-1863-242X

Małgorzata Piekarska-Kasperska
Department of Imaging Diagnostics and Interventional Radiology, Provincial Specialist Hospital of the name Stefan Cardinal Wyszyński in Lublin, al. Kraśnicka 100, 20-718, Lublin, Poland
ORCID ID: 0000-0001-5055-4923

Aleksandra Maciejczyk
Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, 02-097 Warszawa, ul Banacha 1b, Poland
ORCID ID: 0009-0008-5709-0269

Katarzyna Krupa
Wolski Hospital in Warsaw, ul. Kasprzaka 17, 01-211 Warszawa, Poland
ORCID ID: 0009-0006-3120-8631

Julia Błoniecka
Independent Public Healthcare Facility in Garwolin, ul. Lubelska 50, 08-400 Garwolin, Poland
ORCID ID: 0009-0004-0199-6230

Kacper Jankowski
Bielanski Hospital named after Father Jerzy Popiełuszko in Warsaw, ul. Cegłowska 80, 01-809 Warszawa, Poland
ORCID ID: 0009-0000-3722-7805

Anna Daniel
Regional Specialist Hospital in Wrocław - Research and Development Centre, ul. H. M. Kamieńskiego 73a, 51-124 Wrocław, Poland
ORCID ID: 0009-0003-8752-6610

ABSTRACT

Schizophrenia is a complex psychiatric disorder with multifactorial pathophysiology, involving neuroinflammation, oxidative stress, and metabolic disturbances. In recent years, increasing attention has been directed toward the role of diet in modulating mental health, including the onset and progression of schizophrenia. This review explores the potential impact of specific nutrients, dietary patterns, and gut microbiota on schizophrenia-related mechanisms. Evidence suggests that the Mediterranean diet, rich in anti-inflammatory and antioxidant compounds, may exert neuroprotective effects, while the Western diet appears to aggravate inflammatory and metabolic dysregulation. The ketogenic diet has also demonstrated potential benefits through modulation of neurotransmission and mitochondrial function, though its restrictive nature may limit adherence. A central element in these interactions is the gut-brain axis, with the gut microbiota emerging as a key mediator linking dietary factors to central nervous system function. Despite promising findings, current research is limited by a predominance of observational studies. Further randomized controlled trials are needed to assess the therapeutic value of dietary interventions and microbiota-targeted strategies in schizophrenia management.

KEYWORDS

Schizophrenia, Gut Microbiota, Mediterranean Diet, Western Diet, Inflammation

CITATION

Natalia Kraciuk, Alicja Bury, Karol Bartecki, Małgorzata Piekarska-Kasperska, Aleksandra Maciejczyk, Katarzyna Krupa, Julia Błoniecka, Kacper Jankowski, Anna Daniel. (2025) The Role of Dietary Patterns and Nutrients in Schizophrenia: A Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3483

Introduction.

Schizophrenia is a cognitive and behavioral disorder with its probable origin in abnormal development of the human brain due to genetic and environmental factors [1]. This psychiatric disorder affects nearly 23.6 million people worldwide and accounts for an estimated 15.1 million disability-adjusted life years (DALYs), making it a substantial impact on global health and functioning [2]. Schizophrenia symptoms are commonly divided into two groups: positive and negative. Positive symptoms (such as hallucinations, prominent delusions, disorganized thinking and bizarre behavior) reflect an excess or distortion of normal psychological functions. In contrast, negative symptoms involve a reduction or loss of typical behaviors and emotional responses. These include decreased motivation and interest (e.g., avolition, anhedonia, asociality) as well as reduced expressive abilities (e.g., blunted affect, alogia). Negative symptoms are considered a main feature of schizophrenia leading to long-term impairment and social isolation [3,4]. In addition to these symptom domains, cognitive impairments are a core component of schizophrenia, affecting memory, attention, executive functions, and overall information processing [5].

Although complete recovery is achievable in approximately 37.5% of patients with schizophrenia, a substantial proportion of patients experience persistent symptoms despite treatment [6]. On the other hand, a significant number of patients—ranging from 63% to 74%—do not adhere to prescribed antipsychotic medications [7]. Key factors contributing to nonadherence include adverse side effects (such as weight gain, dyslipidemia, glucose dysregulation, and hyperprolactinemia), severity of illness, low insight, low socioeconomic status and quality of life and lack of social support [8,9,10]. These challenges underscore the ongoing need for more effective, tolerable, and accessible treatment strategies aimed at improving long-term outcomes and quality of life for individuals living with schizophrenia.

In recent years, growing attention has been directed toward the potential role of diet and nutritional status in the etiology, progression, and treatment of schizophrenia. Nutrient deficiencies and metabolic disturbances may influence brain function, symptom severity, and treatment outcomes. Therefore, exploring nutritional factors may offer novel, adjunctive strategies for improving patient care.

The aim of this review is to examine recent evidence on the impact of diet on schizophrenia and to evaluate the potential for dietary interventions to support symptom management in affected individuals.

Methodology

A literature search was conducted using PubMed and Google Scholar up to July 2025. Keywords included "schizophrenia," "nutrition," "omega-3 fatty acids," "vitamin D," "oxidative stress," "gut microbiota," and "dietary patterns."

Studies were selected based on relevance to the role of key nutrients, dietary patterns, and gut microbiota in schizophrenia and psychosis. Included were clinical trials, meta-analyses, and systematic reviews published in English, focusing on human populations. Animal studies and non-full-text articles were excluded.

Data were synthesized narratively with emphasis on biological mechanisms linking nutrition and schizophrenia pathophysiology.

Discussion

1. Nutritional Status in People with Schizophrenia

People with schizophrenia present significant nutritional deficiencies that may have an impact on their psychiatric symptoms. The studies have reported that people with schizophrenia and other psychotic episodes compared to the healthy group have low blood levels of vitamin D, vitamin B12 and folic acid [11,12]. Moreover evidence suggests that deficiencies may also extend to essential fatty acids and antioxidants, which are vital for brain development, neurotransmission, and protection against oxidative stress [20-23, 60-62].

In addition to biological mechanisms, poor nutritional status in this population may result from unhealthy dietary habits, cognitive impairments, low socioeconomic status, and the side effects of antipsychotic medications, which often lead to weight gain and metabolic disturbances. These factors can further exacerbate the risk of nutrient imbalances, influencing the course and severity of psychiatric symptoms.

Given the role of specific nutrients in maintaining neuronal health and modulating inflammation, oxidative stress, and neurotransmitter function, the following section explores key nutrients whose altered levels or metabolism may contribute to the pathophysiology of schizophrenia and whose supplementation could offer potential therapeutic benefits.

2. Key nutrients

2.1 Omega-3 fatty acids

The membranes of human brain cells are primarily composed of polyunsaturated fatty acids (PUFAs), particularly omega-3 and omega-6 fatty acids. The omega-3 family includes alpha-linolenic acid (ALA), which serves as a precursor for the synthesis of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [13,14].

DHA constitutes approximately 40% of the phospholipids in brain cell membranes, making it essential for proper brain function—particularly in processes such as memory and learning. It also plays a key role in protecting against brain aging and supporting overall brain development [15–18].

Abnormalities in cell membrane composition have been hypothesized to contribute to the neurodevelopment of schizophrenia [19]. Several studies have shown lower levels of PUFAs in the erythrocyte membrane of patients with schizophrenia compared to healthy controls [20-23]. Moreover some studies have revealed abnormalities of PUFA levels in postmortem brains of schizophrenia patients, however, these changes might be specific for certain regions of the human brain [24-26].

Deficiency of PUFA levels might affect membrane fluidity, thus leading to impairment of neurotransmitter signaling, particularly dopamine and glutamate, which are vital in pathophysiology of schizophrenia [27]. Abnormalities of cell membranes, including those in mitochondria, might also increase the vulnerability of brain cells to oxidative stress, which is observed in patients with schizophrenia. Oxidative stress contributes to impaired neurotransmission and mitochondrial dysfunction, leading to disrupted myelination in the brain [28]. Since dysregulation of dopamine transmission, particularly hyperactivity in limbic pathways and hypoactivity in the frontal lobe and additional mesolimbic structures, is thought to underlie positive and negative respectively, PUFA deficiency may play a vital role in the severity of schizophrenia symptoms [29].

Some studies have shown that supplementation of omega-3 might have a therapeutic potential in schizophrenia patients. Amminger GP et al. conducted two studies with one long-term follow-up that have shown that omega-3 fatty acids reduced conversion rate to psychosis in ultra-high risk patients and improvement in positive and negative symptoms management [30-32]. Studies focusing on early-onset schizophrenia further suggest that omega-3 supplementation might have a positive effect on negative symptoms [33,34]. However, a meta-analysis conducted by Chen et al. has shown that the beneficial role of omega-3 supplementation might be limited to patients in the early stages of schizophrenia. In the prodromal phase, the supplementation was correlated with positive symptom severity reduction and lowering conversion rates of first-episode psychosis. In the first-episode stage, the supplementation was linked to a decrease in non-psychotic symptoms and a reduced need for antipsychotic medication [35].

2.2 Folic acid and vitamin B12

Vitamin B12 and folate are cofactors in one-carbon metabolism, particularly the remethylation of homocysteine to methionine and the synthesis of S-adenosylmethionine (SAM), the universal methyl donor. Therefore, they play a significant role in DNA synthesis and epigenetic regulation [36]. Several studies have shown correlation between schizophrenia and high levels of homocysteine [37-40]. The accumulation of homocysteine might lead to excessive neuronal apoptosis and promote oxidative stress [41,42].

Given the above, deficiency of folate and vitamin B12 might contribute to cognitive impairment and negative symptoms by disrupting methylation pathways, increasing oxidative damage, and impairing neurotransmitter synthesis. Roffman et al. conducted studies that demonstrated reduced levels of folate and vitamin B12 in individuals with schizophrenia compared to healthy control. Moreover, their study showed that B12 and folate supplementation led to improvement in negative symptoms, particularly alogia. However, the treatment response was determined by genetic variation in folate absorption, therefore personalised treatment could be more beneficial [43].

2.3 Vitamin D

Vitamin D3 is a steroid hormone that plays an essential role in various brain functions, including neurodevelopment, regulation of neurotransmission and calcium signaling [44,45]. Its receptors (VDR) and the enzymes required for its activation are widely distributed in the human brain, particularly in regions implicated in the pathophysiology of schizophrenia, such as the prefrontal cortex, hypothalamus, and substantia nigra [46].

A recent meta-analysis conducted by Cui et al. demonstrated that individuals with schizophrenia have significantly lower serum levels of vitamin D compared to healthy controls [47]. This finding suggests the potential role of vitamin D deficiency in pathophysiology of schizophrenia. Furthermore, the epidemiological evidence indicates that schizophrenia occurs more frequently in individuals born in winter or spring and that its prevalence increases with latitude [48,49]. These observations might support the hypothesis that vitamin D deficiency during early brain development may increase the risk of developing schizophrenia in adulthood.

Vitamin D plays a key role in growth and development of dopamine-producing neurons. The evidence suggests that its deficiency during early neurodevelopment may impair expression of significant transcription factors essential for dopamine synthesis, such as Nurr1 and tyrosine hydroxylase. Therefore, vitamin D deficiency may disrupt dopamine signaling pathways [50].

Moreover, it has been shown that vitamin D modulates neuroinflammatory processes in the brain. Its deficiency may increase activation of microglia and elevate production of pro-inflammatory cytokines [51]. Since neuroinflammation is implicated as a contributing factor in schizophrenia, vitamin D may present protective effects through its anti-inflammatory properties [52].

Several studies suggest a potential link between vitamin D deficiency and increased severity of negative symptoms as well as cognitive functions disruption. However, findings across studies remain inconsistent and require further research to clarify the role of vitamin D in schizophrenia symptoms [53,54].

2.4 Antioxidants

Oxidative stress, a key factor in the pathophysiology of schizophrenia, arises from an imbalance between production of reactive oxygen species (ROS) and the body's antioxidant defenses [28]. Excess ROS can damage cellular structures - including lipids, proteins, and DNA - contributing to neuroinflammation, mitochondrial dysfunction, and dysregulation of dopamine and glutamate signaling, all of which are strongly implicated in schizophrenia [55,56].

Redox homeostasis is maintained by enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic molecules (e.g., vitamins C and E, glutathione, polyphenols) [57,58]. Studies have shown reduced activity of these systems in individuals with schizophrenia, which may increase neuronal susceptibility to oxidative damage and contribute to cognitive impairment [59-61].

Dietary antioxidants, like vitamins E and C support redox balance and may have beneficial effects on cognition, although evidence for routine supplementation remains inconclusive [62]. Polyphenols - plant-derived compounds found in fruits, cocoa, and wine - demonstrate antioxidant and anti-inflammatory activity, exert neuroprotective effects, and may modulate the gut microbiota. However, clinical data on their efficacy is limited and require further investigation [63,64].

Given the above, disturbances in the metabolism of key nutrients - such as omega-3 fatty acids, B vitamins, vitamin D, and antioxidants - may contribute significantly in pathophysiology of schizophrenia.

These impairments can affect neurotransmission, inflammatory responses, oxidative stress regulation, and cognitive functioning. While current evidence indicates potential therapeutic benefits of nutrient supplementation, particularly in the early stages of the illness, findings remain inconsistent. Therefore, further large-scale, high quality clinical trials are necessary to assess the efficacy, optimal dosing, and clinical indications for integrating nutritional interventions into standard treatment of schizophrenia.

3. Dietary Patterns

Recent research in nutritional psychiatry has shifted focus from individual nutrients to dietary patterns. This approach captures overall quality and composition of the diet, offering a more valid representation of real-life dietary intake. Since individuals with schizophrenia often exhibit poor dietary habits, this area of research may yield significant findings and inform the development of specific dietary guidelines.

3.1 Mediterranean Diet

The Mediterranean diet (MD), one of the most extensively studied dietary patterns, is considered beneficial for human health in multiple aspects. Numerous studies have demonstrated that adherence to the Mediterranean diet is associated with reduced risk of various conditions, including cardiovascular diseases, overall cancer mortality, metabolic syndrome, and diabetes [65-68]. This broad spectrum of positive health effects has prompted researchers to study its potential impact on neurodegenerative and psychiatric disorders, including schizophrenia.

The term Mediterranean diet refers to the dietary patterns typical of residents of Greece and southern Italy [69]. It is characterised by high intake of plant-based foods, such as vegetables, legumes, fruits, nuts; moderate consumption of dairy products (mainly yoghurt and cheese) and fish; low consumption of red meat. The primary source of fat is olive oil, particularly extra virgin. Additionally, moderate wine consumption during meals is another characteristic feature of the Mediterranean diet [69]. Therefore, the MD provides several key nutrients, such as omega-3 fatty acids (from olive oil, fish, nuts), polyphenols (found in vegetables, red wine, olive oil), and vitamins [70].

Studies have demonstrated that adherence to the Mediterranean diet has a positive effect on cognitive functions and slows cognitive decline [71,72], which is particularly important given the cognitive impairments observed in schizophrenia. This effect may be partly attributed to the neuroprotective properties of its components, particularly anti-inflammatory and antioxidant effects. As mentioned above, chronic inflammation and oxidative stress have been implicated in the pathophysiology of schizophrenia. Moreover, adherence to the MD has been linked to improved weight regulation and metabolic health factors of particular relevance for individuals with schizophrenia, given the high risk of antipsychotic-induced metabolic disturbances [7,8].

Furthermore, recent evidence suggests that Mediterranean diet may positively influence gut microbiota composition [73], which might be important for proper brain function and symptom management in schizophrenia, as will be discussed later in this paper.

Given the above, the Mediterranean diet might be a promising intervention in individuals with schizophrenia through its range of health benefits, such as improved metabolic profile and potential neuroprotective effects. These findings support growing interest in diet-based interventions as treatment strategies in psychiatric care.

3.2 Western Diet

The Western lifestyle is a growing concern for public health worldwide. It is associated with chronic overnutrition, frequent snacking and physical inactivity [74]. Its dietary pattern, the Western diet, is characterised by high intake of nutrition-poor, processed and refined food (such as fast food, sugary drinks and packaged snacks) rich in added sugars and saturated fats, as well as high consumption of red and processed meats [75]. That dietary model has been linked to increased risk of colorectal cancer incidence, cardiovascular disease, type 2 diabetes and obesity [76-78].

There is growing evidence suggesting that the Western diet may have a negative influence on mental health through its proinflammatory effect [79]. This may be attributed to the high content of salt, refined sugars and saturated fat in the Western diet products, which disrupt immune cell homeostasis both directly - by promoting inflammatory cytokine production, activating pro-inflammatory signaling pathways, and impaired phagocytosis - and indirectly, by altering the gut microbiome in favor of pro-inflammatory bacteria strains

over beneficial one. However, studies on gut-microbiota in this context are relatively recent and require further investigation [80-82].

The CHANGE study, which examined dietary patterns in individuals with schizophrenia, demonstrated that patients with schizophrenia tend to exhibit poor dietary habits, such as high intake of fat and refined sugars. [83]. Another study conducted in Japan identified a dietary pattern termed "cereal", characterized by a high intake of fat and refined carbohydrates, which was significantly associated with an increased risk of schizophrenia [84]. These patterns may contribute to elevated systemic inflammation, which could play a significant role in the pathogenesis of schizophrenia and influence symptom severity.

Furthermore, since antipsychotic treatment is known to increase the risk of weight gain and metabolic disturbances [7,8], the association of the Western diet with obesity and metabolic syndrome raises a particular concern for individuals with schizophrenia. The interaction between unhealthy dietary choices and the side effects of pharmacological treatment may contribute to the deterioration of both physical and mental health outcomes.

3.3 Ketogenic diet

In recent years, the ketogenic diet has become one of the most popular dietary trends. The central feature of this dietary pattern is the production of ketone bodies, including acetoacetic acid, beta-hydroxybutyric acid, and acetone, which provide an alternative energy source for the central nervous system (CNS) and peripheral tissues. The ketogenic diet is characterized by a high intake of fats, moderate intake of proteins and very low intake of carbohydrates [85]. Its popularity stems from various potential therapeutic effects both metabolic and neuroprotective. A meta-analysis conducted by Zhou C et al. demonstrated that the ketogenic diet may have a positive effect on weight loss, glycemic control and lipid profile in type 2 diabetes mellitus patients [86]. Additionally, it has been revealed that the ketogenic diet may reduce cardiovascular risk by lowering blood pressure and weight-loss [87]. Moreover, several studies have shown that the ketogenic diet may have beneficial effects reducing seizure frequency in pediatric epilepsy, improving cognitive functions in neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease, and alleviating migraine symptoms [88-91]. Nevertheless, more research is needed to confirm these effects.

The neuroprotective properties of the ketogenic diet, which may be key in addressing the underlying mechanisms of schizophrenia, are mediated through several biological mechanisms. Evidence suggests that the ketogenic metabolism is associated with reduced reactive oxygen species production, suppression of pro-inflammatory cytokine release, and enhanced expression of neuroprotective neurotrophic factors [92]. Additionally, the diet has been linked to a reduction of the demyelination process [93]. Emerging research also points to the potential beneficial effect of ketosis on gut microbiota composition, However, the absence of large-scale randomized trials warrants further investigation in this area [94].

The potential therapeutic effects of the ketogenic may represent a promising treatment strategy in individuals with schizophrenia. However, due to the restrictive nature of this dietary pattern, long-term adherence may be challenging. Therefore, its implementation should be carefully assessed and supervised.

Studies suggest that dietary patterns may influence schizophrenia. The Mediterranean diet exhibits anti-inflammatory and neuroprotective effects, the Western diet exacerbates inflammation and increases the risk of metabolic disturbances, while the ketogenic diet may positively influence cognitive functions, although its implementation should be carefully considered.

4. Gut microbiota and the gut-brain axis

The term "gut microbiota" refers to the diverse community of microorganisms - including bacteria, archaea and eukaryotes - that colonise the human gastrointestinal (GI) tract, with an estimated total number of around 10^{14} microorganisms. This population exceeds the number of human body cells, and their collective genetic material, referred to as the "microbiome", is nearly 150 times larger than the human genome [95,96]. Anaerobic microorganisms are several orders of magnitude more abundant than aerobes, with the majority belonging to two major bacterial phyla: *Bacteroidetes* and *Firmicutes* [95].

The intestinal microbiota plays several crucial roles within the GI tract. One of its primary functions is the fermentation of dietary components that are resistant to host digestive enzymes, particularly dietary fibers. Through this process, the gut microbiota produces short-chain fatty acids (SCFAs), such as acetate and butyrate. SCFAs are key energy sources for colonocytes and peripheral tissues, thus contributing to the production of ketone bodies and carbon dioxide, as well as cholesterol biosynthesis in the liver. Additionally, SCFAs stimulate the secretion of leptin from adipocytes, a hormone involved in regulating appetite and energy balance [97]. Furthermore, the evidence suggests the potential role of gut microbiota in B-vitamin biosynthesis [98].

Another important role of the gut microbiota is its involvement in immune modulation. The aforementioned SCFAs help downregulate the production of pro-inflammatory cytokines, influence peripheral T cells - particularly regulatory T cells - and enhance the integrity of the intestinal epithelial cell (IEC) barrier, thus protecting the systemic circulation from GI-derived toxins. Moreover, SCFAs are essential for maintaining microglia, the resident macrophages of the CNS [99]. Finally, the gut microbiota itself acts as a barrier, preventing pathogenic factors from penetrating the intestinal lining [100]. Given its broad immunological functions, the gut microbiota is often considered the largest lymphatic organ in the human body [101].

In addition to its metabolic and immunological functions, the gut microbiota is a central component of the gut-brain axis - a complex, bidirectional communication system between the CNS and the GI tract. This interaction is mediated by various components, including the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitters, cytokines and SCFAs [102]. The HPA axis, in particular, plays a critical role in coordinating stress responses by regulating cortisol secretion, which can influence gut barrier integrity, microbial composition, and modulate immune function [103]. Beyond hormonal signaling, the gut microbiota contributes to neurochemical communication by producing numerous neurotransmitters, such as gamma-aminobutyric acid (GABA), acetylcholine, serotonin, and dopamine - all essential to both peripheral and central nervous function [104]. Moreover, it participates in tryptophan metabolism, a key precursor of serotonin, thereby influencing mood regulation. Impairment of this metabolic pathway is strongly associated with neuropsychiatric disorders, such as depression, anxiety, and apathy [105].

Furthermore, imbalances in the gut microbiota composition - commonly referred to as “dysbiosis” - may lead to increased permeability of the GI tract, often termed “leaky gut syndrome” (LGS). This condition allows bacterial endotoxins to cross the intestinal barrier and trigger systemic inflammation, which contributes to the damage of host cells, including neurons [106-108]. Thereby, dysbiosis is strongly associated with autoimmune diseases such as inflammatory bowel disease (IBD), type 1 diabetes, celiac disease, as well as colorectal cancer [109]. Moreover, it has been demonstrated recently that gut-microbiota disturbances may be implicated in various neurological and psychiatric disorders, including Alzheimer’s disease, Parkinson’s disease, autism spectrum disorder, and schizophrenia [110].

Given the above, the gut microbiota and gut-brain axis play a key role in integrating the digestive, immune and nervous systems, making them a promising focus of research in psychiatry and personalised medicine. Since gut microbiota composition can be modulated by various interventions, such as probiotics, prebiotics, or faecal microbiota transplantation (FMT) [97], these strategies may offer novel therapeutic approaches for numerous diseases, including schizophrenia.

Conclusions

Emerging evidence highlights the potential role of dietary patterns in modulating the course and symptoms of schizophrenia. Diets such as the Mediterranean and ketogenic patterns show promise due to their anti-inflammatory, antioxidant, and neuroprotective properties, whereas the Western diet may worsen symptom severity through metabolic and inflammatory pathways. The gut microbiota appears to be a key mediator in this relationship. However, most findings are based on observational studies, underscoring the urgent need for well-designed clinical trials to determine the effectiveness, feasibility, and long-term impact of dietary interventions in schizophrenia management.

Author’s contribution

Conceptualisation - Natalia Kraciuk, Aleksandra Maciejczyk, Anna Daniel
Writing - original draft - Natalia Kraciuk, Alicja Bury, Karol Bartecki, Julia Błoniecka
Review and editing - Natalia Kraciuk, Małgorzata Piekarska-Kasperska, Kacper Jankowski, Katarzyna Krupa
Supervision, project administration - Natalia Kraciuk

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