



Major approaches and results of clinical studies of the connection gut microbiota-brain and the effects of nutrients and microorganisms in patients with schizophrenia: a systematic review and meta-analysis

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Abstract

Introduction: Schizophrenia (SZ) affects approximately 20 million individuals worldwide. The gut microbiota (GM) plays a fundamental role.

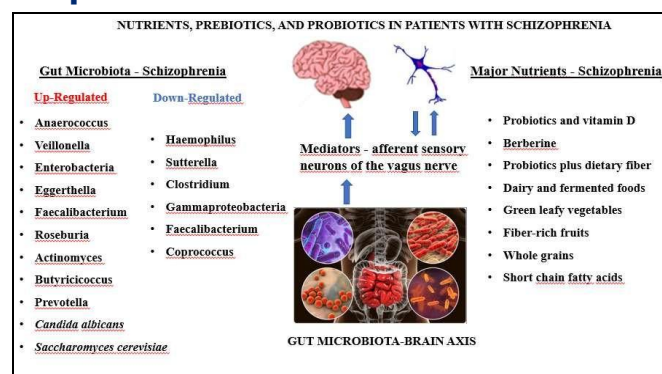
Objective: It was to present, through a meta-analysis, the main considerations and outcomes of clinical studies on the relationship between the gut microbiota-brain axis in patients with schizophrenia, as well as to highlight the effects of nutrients, prebiotics, and probiotics for the improvement of symptoms of schizophrenia. **Methods:** The PRISMA rules for meta-analysis were followed. The research was carried out from November 2024 to January 2025 in the Scopus, Embase, PubMed, Science Direct, and Scielo databases, using scientific articles from 2009 to 2024. The quality of the studies was based on the GRADE

instrument and the risk of bias by the Cochrane (Funnel Plot). **Results and Conclusion:** It was founded 147 studies that underwent eligibility analysis. The final sample had 77 eligible studies and only 69 studies were described in the systematic review. Most studies showed homogeneity in their results, with $I^2 = 15.7\% < 25\%$. The symmetrical funnel plot did not suggest a risk of bias among studies with small sample sizes. Altered gut microbiota composition was evidenced in people with obesity and chronic schizophrenia. The potential role of gut microbiota in schizophrenia is related to changes in brain structure and function. Intestinal serotonin production was potentially associated with an increased risk of schizophrenia. Furthermore, SZ is related to the

reduction of bacteria-producing anti-inflammatory butyrate. Improvement trends in psychiatric symptoms for schizophrenia were observed in men treated with probiotics.

Keywords: Mental health. Mental illness. Schizophrenia. Gut microbiota. Nutrients. Probiotics. Prebiotics.

Graphical Abstract



Source: Own authorship.

Introduction

In the panorama of mental illnesses, schizophrenia (SZ) affects more than 20 million people worldwide, with a mortality rate approximately 3 times higher and a life expectancy reduced by up to 25 years, due to the increased incidence of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) [1-3]. In this context, it is known that antipsychotics (APs) can further aggravate the risks of CVD and T2DM in patients with schizophrenia spectrum disorders [4-7]. In this scenario, the human gut microbiota (GM) contains approximately 100 trillion microorganisms that encode more than three million genes and are more organized than the human genome.

In this scenario, in the Firmicutes species, the main genera are Clostridium, Lactobacillus, Bacillus, Enterococcus, and Ruminococcus. The Bacteroides and Prevotella genera are the main genera of the Bacteroidetes phylum [8]. As a result of this, the GM is essential for regulating digestion, immunity, and metabolic homeostasis [8-14], as well as intestinal permeability, decreased epithelial integrity, and the integrity of the blood-brain barrier (BBB) [14,15]. Furthermore, GM plays a fundamental role in the digestive process, immunological processes, and metabolic control [10,11]. The brain communicates with the GM in a bidirectional manner through neuroendocrine and neuroimmune pathways, constituting the gut microbiota-brain axis (GMBA) [14,16].

In this regard, it is important to note that the vagus nerve is responsible for bidirectional communication in the gut-brain axis through cholinergic activation of nicotinic receptors [17]. This occurs through the afferent sensory neurons of the vagus nerve that transmit stimuli [18,19], controlling motility, secretion, permeability, and immune response [20].

In addition, GMBA needs to be regulated for the hypothalamic-pituitary-adrenal (HPA) axis [21,22]. In this regard, the neuro-immuno-endocrine functions of GMBA are regulated by short-chain fatty acids (SCFA), tryptophan metabolites, and secondary bile acids (deoxycholic acid, ursodeoxycholic acid, and lithocholic acid) [23-25]. GMBA also secretes serotonin (5-HT), dopamine, norepinephrine, and γ -aminobutyric acid (GABA), directly impacting behavioral control in humans [23,26-28].

As a result, HPA axis dysfunction and alterations in GMBA composition have been associated with depression [29], bipolar disorder [30], and schizophrenia [17, 31-36]. Furthermore, alterations in GMBA composition are related to altered glutamate neurotransmission [37], cognitive impairments in schizophrenia, glucose homeostasis, and energy balance [38,39]. Given this, several prebiotics and probiotics are prescribed to mitigate the symptoms of schizophrenia [40,41], as well as to reduce the adverse metabolic effects associated with the use of antipsychotics [42-47]. Studies have shown that changes in GM are observed in patients with schizophrenia. However, longitudinal studies are still needed to conclude causal associations. Thus, prebiotics and probiotics can regulate (rebalance) GM in metabolic disorders and cognitive deficits [48-50].

Therefore, this study aimed to present, through a meta-analysis of the literature, the main approaches and clinical results of the relationships between the intestinal microbiota-brain axis in patients with schizophrenia, highlighting the main nutrients, prebiotics, and probiotics in mitigating the symptoms of schizophrenia.

Methods

Study Design

This study followed the systematic review and meta-analysis standard, following the PRISMA rules [51]. Table 1 represents the descriptors of the present study, following the PICOS (Patients; Intervention; Control; Outcomes, and Study Design) literary search strategy.

Table 1. Literary search strategy (PICOS).

PATIENTS	Participants diagnosed with schizophrenia
INTERVENTIONS	Nutrients, prebiotics, and probiotics
CONTROL	Participants without schizophrenia
OUTCOMES	Improvement of schizophrenia symptoms
TYPES OF STUDIES	Meta-analysis, systematic reviews, randomized, controlled, cohort, case-control, observational clinical studies

Data Sources and Research Strategy

The following descriptors (MeSH Terms) were used: Mental health. Mental illness. Schizophrenia. Gut microbiota. Nutrients. Probiotics. Prebiotics. The studies were collated from February to April 2024 in the Web of Science, Scopus, PubMed, Embase, Ovid, Science Direct, Scielo, and Google Scholar databases, recruiting clinical studies from 2009 to 2024 through the use of the Boolean terms "OR", "AND" and the operator "NOT" was used to target scientific articles of interest. Table 2 shows the search structure in PubMed.

Table 2. For example, in the search structure in PubMed, the same search strategy was used in the other databases.

PubMed	<i>Mental health OR Mental illness OR Schizophrenia</i>
	AND
PubMed	<i>Gut microbiota OR Nutrients OR Probiotics OR Prebiotics</i>
	AND
	<i>Prospective Clinical studies OR Retrospective Clinical studies OR Randomized clinical trials OR Clinical case series</i>
	NOT
PubMed	<i>Editorials OR Short communications OR Case Report</i>

Methodology for analyzing the quality of studies, eligibility, and risk of bias

The analyzed studies were previously listed after the scientific quality criteria according to the GRADE classification [52]. High-quality evidence was attributed to randomized controlled clinical trials (RCTs) and with a sample size that offers reliable statistical analysis. It was also performed with an analysis of the methodological quality of AMSTAR-2. Available at: <https://amstar.ca/>. It was accessed on: 03/16/2024. The Cochrane Instrument [53] was adopted to assess the risk of bias in the chosen studies using the Cohen Test, producing the Funnel Plot graph.

Data Analysis

Stata 18 and Minitab 21 software were used to process the data resulting from this study. Cohen's test was performed to calculate the effect size and the inverse of the standard error (sample size) to establish whether there was a risk of bias through the analysis of the graphical symmetry of the studies in the Funnel Plot. Also, a forest plot showing the effect of probiotics on schizophrenia treatment through odds ratio (OR) analysis. The Heterogeneity Test (Chi-Square Test - X^2) was also performed on the results of the studies, adopting $X^2 > 50\%$ with homogeneous results between studies, and $p < 0.05$ with no statistically significant difference, in the 95% CI. The analyzes followed Pearson's Chi-square test, with $p < 0.05$ with statistical significance of association, with a confidence interval (CI) of 95%.

Results

Summary of Literary Findings

After the selection process of the aforementioned studies, a total of 147 articles were compared. After removing duplicate articles and articles that did not meet the scope of the present study, a total of 107 articles were analyzed according to the GRADE classifications and the AMSTAR-2 methodological quality analysis. After this, 77 studies were fully evaluated, removing 10 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2. The 69 studies (a total of 2,879 participants) were described in the meta-analysis and presented homogeneity in their results, with $X^2 = 67.7\% > 50\%$ (Figure 1).

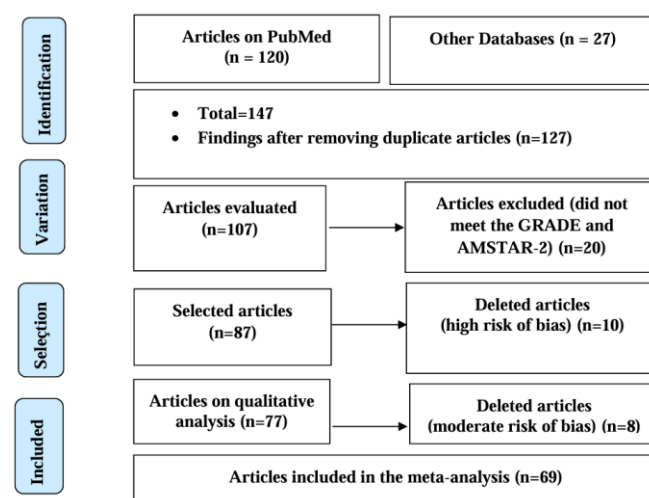


Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Table 3 shows the results on the correlation between the gut microbiota of Schizophrenic Patients vs. Healthy Patients by the Chi-Square method (X^2),

effect Size (difference of the magnitude), and precision (1/Standard Error or sample size). Most studies included in the meta-analysis showed statistical differences between the gut microbiota results of Schizophrenic Patients vs. Healthy Patients, with $p > 0.05$. Only studies in references 7, 8, 9, 14, 15, and 16 did not show a statistically significant difference between the gut microbiota results of Schizophrenic Patients vs. Healthy Patients, with $p < 0.05$.

Table 3. Results on the correlation between Schizophrenic Patients vs. Healthy Patients by the Chi-Square method (χ^2), with $p < 0.05$ without statistical difference, at 95% CI. The Effect Size (Difference of Magnitude) was calculated using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error).

Authors N=69	Schizophrenia related to alteration of the gut microbiota	Effect Size	1/Standard Error
References	Schizophrenic Patients vs. Healthy Patients (p-value)	Difference of Magnitude (Cohen Test- d)	Precision and Sample Size
1.	0.345>0.05	0.0120	8.4
2.	0.241>0.05	-0.0122	8.8
3.	0.214>0.05	0.0130	8.1
4.	0.312>0.05	-0.0131	7.8
5.	0.425>0.05	0.0120	7.7
6.	0.523>0.05	-0.0130	8.9
7.	0.023<0.05	0.1050	2.9
8.	0.027<0.05	-0.1000	3.5
9.	0.044<0.05	0.1000	3.8
10.	0.567>0.05	0.0150	8.0
11.	0.455>0.05	-0.0150	8.2
12.	0.067>0.05	0.1200	4.1
13.	0.055>0.05	-0.1200	4.2
14.	0.021<0.05	0.1300	3.7
15.	0.032<0.05	-0.1300	4.0
16.	0.011<0.05	0.1250	2.9
17.	0.211>0.05	-0.1250	3.2
18.	0.344>0.05	0.0090	8.5
19.	0.444>0.05	0.0120	8.4
20.	0.239>0.05	-0.0100	8.8
26.	0.553>0.05	0.0130	8.1
27.	0.368>0.05	-0.0170	7.8
28.	0.472>0.05	0.0210	7.4
29.	0.581>0.05	0.0160	8.9
30.	0.673>0.05	0.0230	8.3
31.	0.233>0.05	-0.1000	3.5
32.	0.467>0.05	0.1000	3.8
33.	0.776>0.05	0.0150	8.0
34.	0.689>0.05	-0.0150	8.2
35.	0.567>0.05	0.1200	4.1
36.	0.489>0.05	-0.1200	4.2

37.	0.655>0.05	0.1300	3.7
38.	0.766>0.05	-0.1300	4.0
39.	0.588>0.05	0.1250	2.9
40.	0.066>0.05	-0.1250	3.2
41.	0.378>0.05	0.0090	8.5
42.	0.078>0.05	0.1100	3.8
43.	0.588>0.05	0.0110	8.1
44.	0.756>0.05	-0.0090	8.3
45.	0.345>0.05	0.0140	7.1
46.	0.467>0.05	-0.0150	7.0
47.	0.488>0.05	0.0190	6.7
48.	0.599>0.05	0.0160	6.9
49.	0.678>0.05	-0.1300	3.5
50.	0.234>0.05	-0.1100	3.3
54.	0.345>0.05	0.1100	3.4
55.	0.055>0.05	0.1300	4.3
56.	0.057>0.05	-0.1300	4.5
57.	0.064>0.05	0.1300	4.7
58.	0.079>0.05	-0.1200	4.2
59.	0.123>0.05	0.1230	3.1
60.	0.066>0.05	-0.1230	3.0
61.	0.678>0.05	0.0070	9.0
62.	0.088>0.05	0.1200	3.5
63.	0.699>0.05	0.0020	9.1
64.	0.899>0.05	-0.0030	8.9
65.	0.875>0.05	0.0100	7.3
66.	0.789>0.05	-0.0015	8.5
67.	0.955>0.05	-0.0012	9.2
68.	0.967>0.05	0.0014	9.0
69.	0.788>0.05	0.0015	8.5

Source: Own authorship.

The results of the Funnel Plot graph showed symmetry (no risk of bias) between the studies with small sample sizes (Base of the graph highlighted by the circle) (Figure 2).

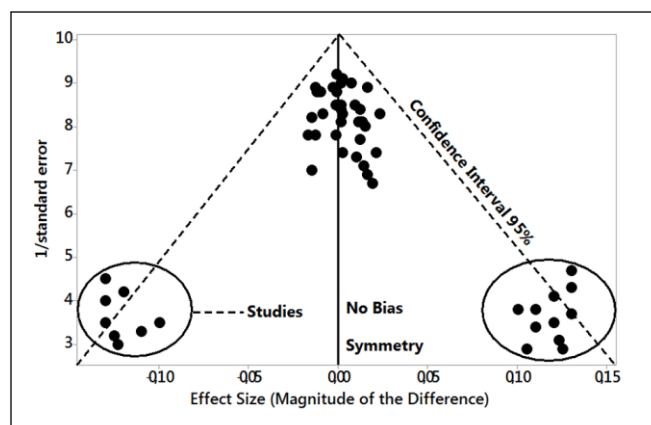


Figure 2. Funnel Plot analysis shows the absence of risk of bias among the studies with small sample sizes at the base of the graph, at the 95% CI. Source: Own Authorship.

Patients with obesity and schizophrenia who received nutritional therapy and probiotics had an increased probability of reducing cardiovascular comorbidities and reducing symptoms of the schizophrenia spectrum, with an overall OR=3.52 (CI: 1.22 – 5.78) (Figure 3).

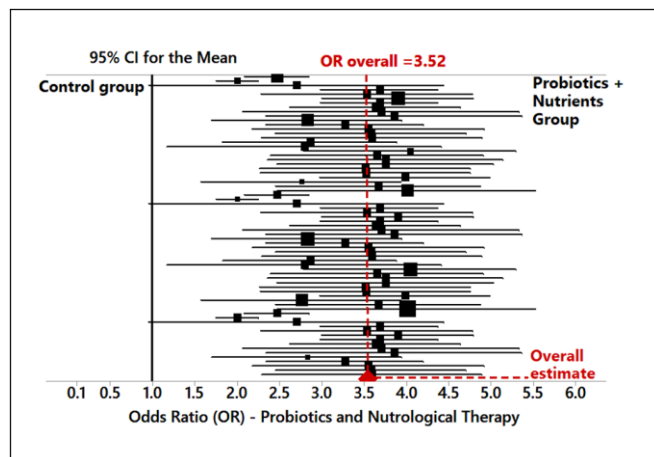


Figure 3. Forest-plot showing the effect of probiotics on schizophrenia treatment. Source: Own Authorship.

Major Clinical Findings and Discussion

The present study analyzed the main approaches and clinical results of the relationships between the gut microbiota-brain axis in patients with schizophrenia, highlighting the main nutrients, prebiotics, and probiotics in mitigating the symptoms of schizophrenia. Most studies included in the meta-analysis showed statistical differences between the gut microbiota results of Schizophrenic Patients vs. Healthy Patients, with $p > 0.05$. Only studies in references 7, 8, 9, 14, 15, and 16 did not show a statistically significant difference between the gut microbiota results of Schizophrenic Patients vs. Healthy Patients, with $p < 0.05$, as these studies had a small sample size, which made the sensitivity of the analyses difficult.

Also, this study showed that nutritional therapy and probiotics had an increased probability of reducing cardiovascular comorbidities and reducing symptoms of the schizophrenia spectrum, with an overall OR=3.52 (CI: 1.22 – 5.78), according to Figure 3.

Through the analysis and interpretation of the studies selected in this study, it was evidenced that the gut microbiota (GM) and the brain communicate through several pathways, including the immune system, tryptophan metabolism, the vagus nerve, and the enteric nervous system [1-20], through microbial metabolites, such as short-chain fatty acids, branched-chain amino acids, peptidoglycans, and microRNAs [26-40]. Recent studies have observed the relationship between GM imbalance and the occurrence of autism, anxiety, obesity, schizophrenia, Parkinson's

disease, and Alzheimer's disease [40-50,54].

In this context, a study carried out by the authors Nguyen et al. (2019) [55] investigated the composition of GM in 50 individuals, including 25 people with chronic schizophrenia (CSZ) and 25 individuals without chronic schizophrenia (WSZ). Stool samples were analyzed by 16S rRNA sequencing. A significant difference in the composition of GM was observed between the two groups of subjects. It was shown that Proteobacteria are relatively reduced in individuals with schizophrenia compared to WSZ. At the genus level, Anaerococcus had a relatively increased incidence of schizophrenia, while Haemophilus, Sutterella, and Clostridium decreased. Furthermore, Bacteroides has been associated with worse depressive symptoms and Coprococcus has been associated with a greater risk of developing coronary heart disease.

Based on these findings, GM has an important role in communicating with brain functions via the vagus nerve, and consequently in schizophrenia. To corroborate this, a meta-analysis study analyzed strategies to regulate GM for the treatment of schizophrenia. The results showed no effect of D-cycloserine (10 studies), minocycline (7 studies), other antibiotics (2 studies), probiotics alone (1 study), and artemisinin (1 study) on negative symptoms of schizophrenia when compared to placebo. Furthermore, negative symptoms were evidenced for sodium benzoate (2 studies), artemether (1 study), and probiotics combined with vitamin D (1 study) when compared to placebo [56].

Authors Li et al., 2021 [57] performed 16S rRNA sequencing with MRI to investigate discrepancies in the stool microbiota of thirty-eight SZ patients and thirty-eight normal controls (NC). The relative amount of Ruminococcus and Roseburia was significantly lower, while the presence of Veillonella was substantially higher in patients with SZ. The authors Zuhuanget et al. (2020) [58] analyzed the relationships between GM, metabolites, and neuropsychiatric disorders as SZ through a randomized clinical study. The family Enterobacteriaceae and the order Enterobacteria may contribute to a significantly increased risk of SZ, except for the class Gammaproteobacteria. The gut hormone serotonin was significantly associated with an increased risk of SZ.

Additionally, a meta-analysis study by authors Nikolova et al. (2021) [59] analyzed GM changes in adult psychiatric populations. A total of 34 studies revealed alpha diversity ($n=1,519$ patients, $n=1,429$ control participants). A significant reduction in GM richness was observed in SZ patients compared to controls. Differences in beta diversity were significantly observed for major depressive disorder, psychosis, and

schizophrenia. A reduction in *Faecalibacterium* and *Coprococcus* and enriched levels of *Eggerthella* were found among major depressive disorder, bipolar disorder, psychosis, schizophrenia, and anxiety, indicating that these pathologies reflect the reduction of bacteria producing anti-inflammatory butyrate that maintains mucosal integrity, reduction of macrophages and pro-inflammatory cytokines, and at the same time increase in anti-inflammatory factors [60-62]. However, the *Lactobacillus* genus (probiotics) was present in high amounts in schizophrenia [63]. One study identified increased psychosis and schizophrenia in subspecies that are not normally present in the healthy gut [64]. Increased *Lactobacillus* has been associated with the use of antipsychotics [65].

Among the numerous clinical and demographic factors that may have contributed to the widespread inconsistencies between studies, current evidence allowed us to explore 2 main characteristics: geographic region and psychiatric medication. Geographic regions and associated dietary factors can profoundly affect GM composition [66-70].

Based on this, healthy rebalancing of GM with probiotics is an important therapeutic strategy to treat the gastrointestinal comorbidities and psychiatric symptoms of SZ. In this sense, *Candida albicans* and *Saccharomyces cerevisiae* are elevated in SZ. In a longitudinal, double-blind, placebo-controlled pilot investigation of 56 outpatients with SZ, the impact of probiotic treatment on antibody levels against these fungi was evaluated. Probiotic treatment was shown to significantly reduce antibodies against *C. albicans* over the 14-week study period in men but not in women. Antibody levels against *S. cerevisiae* were not changed in either treatment group. The highest levels of intestinal discomfort over time occurred in *C. albicans*-seropositive men who received the placebo. A reduction in psychiatric symptoms of SZ was evidenced in 384 men treated with probiotics who were seronegative for *C. albicans* [71].

Authors Pu et al. (2021) [72] analyzed through an RCT study the effects of berberine on GM in 132 schizophrenic patients with mild metabolic disorders induced by olanzapine for 9 months. As a result, fasting blood glucose, insulin resistance (HOMA-IR), glycated hemoglobin (HbA1), triglycerides, and BMI were significantly lower in patients receiving berberine compared to placebo after 12 weeks of treatment. The abundance of firmicutes and coliforms was significantly lower and the abundance of *Bacteroides* was significantly higher in patients receiving berberine compared to placebo after 12 weeks of treatment.

The authors Sevillano-Jiménez et al. (2022) [73] analyzed, through a randomized clinical trial study (two

arms, double-blind, balanced block, six-month intervention) the influence of increased intake of prebiotic and probiotic foods on the cardiometabolic state in individuals with SZ in the context of COVID-19. This study was carried out on a group of 50 individuals diagnosed with schizophrenia spectrum disorder during the SARS-CoV-2 confinement period. In the intervention group, an individual nutritional education program was established with a high content of prebiotics and probiotics (dairy and fermented foods, green leafy vegetables, fiber-rich fruits, whole grains, etc.). Data on cardiovascular status were collected at baseline, three, and six months. A total of 44 completed follow-ups were analyzed. A statistical difference was observed in the anthropometric results at the beginning of the study and six months of intervention. There was also a 27.4% reduction in the prevalence of risk factors for metabolic syndrome, with a decrease in cardiovascular risk in the intervention group at six months.

Still in this sense, another randomized study evaluated the effect of probiotics plus dietary fiber on weight gain induced by antipsychotics. In the first study (90 participants receiving olanzapine plus probiotics or olanzapine monotherapy for 12 weeks), no statistically significant difference in weight gain was observed. Furthermore, the insulin resistance index was lower in the olanzapine plus probiotics group compared with the olanzapine monotherapy group at week 12 (estimated mean difference, -0.65 [95% confidence interval (CI), -1.10 to 0.20]; $p=0.005$). In the second study (60 participants), the increase in body mass (weight increase in kg) was less in the probiotics plus dietary fiber group than in the olanzapine monotherapy group at week 12 (estimated mean difference, -3.45 kg [95% CI, -5.91 to -1.00]; $p = 0.007$) [74].

Also, the authors carried out a randomized, double-blind clinical study, with a 6-month intervention in 50 individuals diagnosed with SZ spectrum disorder, with only 44 individuals completing this study, demonstrating the importance of dietary advice in increasing the intake of synbiotics nutritional status, and eating habits. The control group received only dietary guidance. The intervention group received nutritional education to increase prebiotic and probiotic intake. After 6 months of intervention, a statistical difference was observed in anthropometric results, as well as an increase in the consumption of foods with a high content of synbiotics. Thus, investing in nutritional education and counseling results in improved quality of life in patients with SZ [75].

Finally, authors Ling et al. (2022) [76] developed an observational clinical study with 161 samples,

including 90 samples from elderly patients with SZ and 71 samples from healthy controls through GM analysis (V3-V4 region of the 16S rRNA gene). The results showed that bacterial β diversity analyses are different in patients with SZ and healthy controls. Differences in the composition of bacteria associated with SZ were identified, including *Faecalibacterium*, *Roseburia*, *Actinomyces*, *Butyrivibrio*, and *Prevotella*. A considerable increase in the levels of pro-inflammatory cytokines, such as IL-1 β , was observed in patients with SZ, while the levels of anti-inflammatory cytokines, such as IFN- γ , decreased markedly. Also, the increase in lipopolysaccharide biosynthesis, folate biosynthesis, lipoic acid metabolism, decreased bile acid biosynthesis, and fatty acid biosynthesis in the microbiota associated with SZ can be used by bacteria to produce immunomodulatory metabolites.

Limitations

Despite the important clinical findings of the beneficial action of nutrients, probiotics, and prebiotics in schizophrenia, with emphasis on butyrate-producing bacteria, the present studies found limitations in the world literature such as few randomized clinical studies with methodological scientific rigor, as well as a lack of clinical studies multicenter to be able to better understand the action of nutrients, probiotics, and prebiotics on the gut microbiota of patients from different geographic locations and, finally, there is a limitation of responses from studies on the effects of other drugs (in addition to olanzapine) concomitantly with probiotics to the treatment of schizophrenia.

Conclusion

It was concluded that the potential role of gut microbiota in schizophrenia is related to changes in brain structure and function. The genetically enhanced Enterobacteriaceae family and order Enterobacteria were potentially associated with an increased risk of SZ. Intestinal serotonin production was potentially associated with an increased risk of schizophrenia, mainly in patients with obesity. Furthermore, SZ is related to the reduction of bacteria-producing anti-inflammatory butyrate. Improvement trends in psychiatric symptoms for schizophrenia were observed in men treated with probiotics, as well as an association between seropositivity for *C. albicans* and worse positive psychiatric symptoms. The development of a nutritional program focused on increasing the dietary content of prebiotics and probiotics can effectively improve the cardiometabolic profile in SZ spectrum disorders.

CRedit

Author contributions: **Conceptualization** – All authors; **Data curation** - All authors; **Formal Analysis**- IJZF and DRF.; **Investigation**- All authors; **Methodology** - All authors; **Project administration**- I.J.Z.F.; **Supervision**: I.J.Z.F., D.R.F.; **Writing - original draft**- All authors; **Writing-review & editing**- All authors.

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Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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