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Research Article

Role of Probiotics in Metabolic Response in Schizophrenia: A Randomized Double-Blind Placebo-Controlled Study

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Abstract

Pharmacological interventions used in the treatment of severe mental disorders are leading to secondary conditions such as weight gain and metabolic syndrome. Introducing probiotics as an add on therapy is observed to aid in improving metabolic parameters such as blood sugars and lipid profile. The present study was conceived to understand the role and impact of probiotics on clinical and metabolic profiles in patients with schizophrenia spectrum disorder using a randomized double-blind placebo-controlled design. A total of 100 patients with moderately severe psychosis (PANSS ≥ 50) and deficit in one of the cognitive domains (<15th percentile in NIMHANS neuropsychological battery) were recruited. The participants were randomly allocated to receive either probiotic compound or placebo 2 sachet/day or 3 months. Primary outcomes were evaluated by measuring the changes in basic body functions and blood investigations from baseline to 12 weeks. Secondary outcomes measures assessed changes in PANSS scores at 4th, 8th and 12th weeks and improvement in cognitive symptoms (executive function, attention and memory) at 12 weeks. The side effects were recorded using an adverse events report. The results indicate statistically significant differences in the metabolic profiles (Fasting Insulin: p value = 0.042; Cholesterol: p value = 0.040) and in the positive symptoms (p = 0.039) among participants in the intervention group. Probiotics were found to have an impact on the metabolic functions but there was no significant difference observed in the levels of Brain Derived neurotropic factor levels.

Keywords: Schizophrenia; Probiotics; Metabolic response; Cognitive functions; BDNF

Introduction

Probiotics composed mainly of the genus lactobacillus and Bifidobacterium is a supplement used as an adjuvant intervention to treat secondary conditions of several mental health disorders [1]. Microbiota-Gut-Brain Axis (MGBA) and probiotics have been associated in terms of microbiota modulation [2]. Schizophrenia is a complex brain disorder and antipsychotics used to treat and manage schizophrenia cause significant weight gain and metabolic syndrome [3,4]. This weight gain is primarily caused by the antagonism of histamine H1 and 5-HT2C receptors and partly because of alteration of gut microbiome [5]. Drug induced metabolic dysregulations such as hyperglycemia and hyperlipidemia, could further lead to poor adherence and also cause substantial medical morbidities such as diabetes, cardiovascular disease, stroke and premature death [6]. Further, this drug induced obesity can result in high levels of Free Fatty Acids (FFA) and inflammation, which can cause insulin resistance, and antipsychotics can cause direct damage to β-cells, leading to dysfunction and apoptosis of β-cells that increase insulin resistance [7]. Studies on the combination of Lactobacillus Rhamnosus and Bifidobacterium Lactis Bb12 in Schizophrenia using a randomized, placebo-controlled trial for 14 weeks found that there is a trend increase in plasma BDNF but no change in the PANSS scores and reported less severe bowel movement difficulties [3]. The results of using Probiotic supplement with Vitamin on patients with schizophrenia showed substantial reduction in the symptoms and inflammation, decreased levels of CRP, enhanced antioxidant capacity of plasma and improvement in the PANSS scores. Evidence from recent studies indicate improved metabolic effects of antipsychotic medications and bowel movement regulation as the known benefits of probiotics but suggest further clinical validation for the role of probiotics in the treatment of schizophrenia [8]. Therefore, this Randomized Controlled study (RCT) was conceived to evaluate the impact of adjuvant probiotics intervention on clinical and metabolic profiles in patients with Schizophrenia.

Materials and Methods

Study design and participants recruitment

This was 12 weeks, randomized, double-blind, parallel-group, placebo-controlled study to examine the efficacy of adjuvant probiotics, in reducing antipsychotics induced metabolic disturbances, symptom severity and improving cognitive symptoms, in patients diagnosed with Schizophrenia. The trial's protocol complies with the Standard Protocol Items Recommendations for Intervention Trials (SPIRIT) statement [9]. The study was approved by the Institutional Ethics Committee and was prospectively registered in the clinical trials registry India on 1st June 2022 (CTRI/2022/06/042960). Patients with a primary diagnosis of schizophrenia spectrum disorder were screened against the inclusion and exclusion criteria from the inpatient and outpatient departments of Schizophrenia Research Foundation, Chennai, India from June 2022 to January 2023. A total of X eligible patients was approached, out of which 100 participants consented to participate in the study. Each participant was described about the study, and a witness, typically the patient's caregiver, was present during this explanation and their written informed consent was

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obtained. Participants were randomized to receive either Probiotics supplement or placebo for 3 months. Study participants were assessed at baseline, 4th week, 8th week and at the end of the trial period (12 weeks from baseline).

Randomization and blinding

After screening and obtaining informed consent, a total of 100 participants were randomized to either arm in a 1:1 ratio by an independent researcher. A computerized random number generator was used for randomization of codes, using permuted block-randomization technique [10]. Both the placebo and Probiotics containers were pre-numbered with codes and the coded containers were indistinguishable from each other in appearance (dimensions, weight, color and taste), to conceal treatment allocation and blinding. The patients, rater, research assistants, project investigators, laboratory assistants, and statistician remained blinded throughout the entire trial. Treating clinicians were also blinded to group allocation to ensure that the trial treatment did not influence clinical care. All data were labeled with an alpha-numeric code in line with established protocols currently being used for other clinical trials. All of the trial's data, including biological samples, were kept in a secure location under appropriate storage conditions. Table 1 depicts the time frame of enrollment, allocation, and assessments in SPIRIT format [9] (check supplementary material).

Table 1: Represents the Frequency Distribution of the Data for both intervention and placebo groups.

Variables		Group			
		Placebo		Intervention	
		N	%	N	%
Sex	Male	26	0.52	31	0.62
	Female	24	0.48	19	0.38
Age	18-30	15	0.3	19	0.38
	31-50	35	0.7	31	0.62
Education	School	21	0.42	22	0.44
	College	29	0.58	28	0.56
Marital Status	Unmarried	35	0.7	29	0.58
	Married	13	0.26	16	0.32
	Divorced	2	0.04	5	0.1
Employment Status	Unemployed	38	0.76	28	0.56
	Employed	12	0.24	20	0.4
	Student	0	0	2	0.04

Inclusion and exclusion criteria

Screening of participants were carried out against the following criteria,

Inclusion criteria: Participants were considered eligible for inclusion if they met all the following criteria, (a) Patients aged 18-45 years; (b) Primary diagnosis of a schizophrenia spectrum disorder (schizophreniform, schizophrenia, schizoaffective, psychosis not otherwise specified) with active psychotic symptoms using ICD -10; (c) ICD -10 diagnosis of schizophrenia any type or schizoaffective disorder with disease duration of at least 2 years (2-10 years duration of illness); (d) Education of 9th standard/grade and above; (e) Scores on the Positive and Negative Syndrome Scale (PANSS) indicative of at least moderately severe psychosis (total PANSS score ≥ 50) [11]; (f) Cognitive deficit below 15th percentile in any one cognitive domain of National Institute for Mental Health and Neurosciences (NIMHANS) Neuropsychological battery [12]; (g) Willing to participate in the study.

Exclusion criteria: Participants were excluded if they met at least one of the following criteria, (a) Patients who are uncooperative due to the severity of the illness; (b) Existence of a serious medical/neurological disorder, known allergic to Probiotics; (c) Patients with diagnosis of mental retardation; (d) Primary diagnosis of substance abuse or dependence within the last 3 months; (e) Participated in any investigational drug trial in the past 30 days; (f) Women who were currently pregnant, planning to get pregnant/breastfeeding; (g) Not consenting to participate in the study.

Sample size

Previous studies indicated that the placebo group demonstrated an insulin resistance value of 2.1, whereas the intervention group showed a value of 2.7, both measured using HOMA-IR. To achieve a statistical power of 80% and a 2-sided confidence interval of 95%, a sample size of 25 participants was calculated for each arm, resulting in a total of 50 participants. Considering an estimated attrition rate of 20%, the final total sample size was adjusted to 67, which were then rounded off to 100 (50 participants in each arm).

Interventions

Participants were randomly assigned to one of two groups: Probiotics group or placebo group. The Probiotics group received a daily dosage of 2 grams of a probiotic blend, containing six strains of probiotics (Bacillus Coagulans Unique IS-2, Lactobacillus Rhamnosus UBLR-58, Bifidobacterium breve UBBBr-01, Bifidobacterium Lactis UBBLa-70, Bifidobacterium infantis UBBI-01, and Lactobacillus Plantarum UBLP-40), with 250 mg of L-glutamine. The probiotic blend consisted of 10 billion CFU (Colony-Forming Units). The supplement was provided in the form of sachet powder, with each sachet containing 1 gram of the supplement. Participants were instructed to consume 2 sachets per day (day and night), totaling a daily intake of 2 grams, for duration of 12 weeks (3 months). The supplements were stored in a dry place under 6 degrees centigrade. To ingest the supplement, subjects were advised to mix the powder thoroughly into a cup of water. Participants were advised to not take other vitamin and probiotic supplements and adhere to their regular dietary and physical activity routines. To ensure compliance with the intervention and monitor for any adverse events, weekly telephonic interviews were conducted.

Clinical assessments

Baseline data collection included socio-demographic information and relevant clinical variables using a semi-structured proforma. Assessments covered demographics, anthropometric measurements (weight, height, BMI, waist circumference), vital signs (Blood pressure, Pulse rate) and PANSS scores [11]. Psychiatric assessments (PANSS) and anthropometric measurements and vital signs were conducted monthly (every 4 weeks), while cognitive assessment took place at baseline and 12 weeks. Blood sample collection for fasting insulin, fasting glucose, hs CRP, lipid profiles, and serum BDNF levels at baseline and 12 weeks. Weekly contact with participants allowed for monitoring adherence and adverse events.

Safety

Safety was evaluated using the adverse events reporting form which includes vital signs monitoring (blood pressure, pulse rate, weight, and waist circumference). Adverse events and vital signs monitoring were systematically evaluated at each visit (baseline, 4th, 8th, endline) using a checklist. Table 2 depicts the time frame for assessments of parameters included in the safety monitoring schedule (check supplementary material).

Table 2: Represents comparison of Vital Signs between the intervention and placebo groups.

Effect	Estimate (95% CI)	P value
Body Mass Index		
Time*Group	-0.17 (-0.39,0.04)	0.114
Systolic Blood Pressure		
Time*Group	-0.21(-1.08,0.66)	0.632
Diastolic Blood Pressure		
Time*Group	0.21(-0.51,0.93)	0.572
Pulse rate		
Time*Group	-1.84(-2.85, -0.84)	<0.001

The intervention group has a -1.84 Beats Per Minute (bpm) greater reduction in pulse rate over time compared to the placebo group, and this difference is statistically significant (p-value <0.001).

Outcome measures

A semi structured proforma designed to collect information regarding the socio demographic data, illness and treatment related variables. Vital signs monitoring- Blood pressure and Pulse rate at all visits.

Primary outcomes: a) Anthropometric assessments- weight, height, BMI, waist circumference at baseline, 4, 8 and 12 weeks. BMI is calculated as weight in kilograms divided by height in meter squared) Metabolic profiles- Blood pressure, fasting blood glucose, lipid profiles, fasting insulin & insulin resistance will be done at baseline and at 12 weeks, and insulin resistance was calculated based on a formula of homeostatic model assessment for insulin resistance (HOMA-IR) [13], by fasting insulin [microU/L] x fasting glucose [nmol/L]/22.5. Serum BDNF using ELISA and CRP levels will be done at baseline and 12 weeks.

Secondary outcomes: a) Positive and Negative syndrome Scale for assessment of Positive and Negative Symptoms (PANSS) will be done at baseline, 4, 8 and 12 weeks. The PANSS is a 30-items rating scale composed of validated subscales to assess negative (7 items), positive (7 items), and general psychopathological (16 items) signs of schizophrenia [11]. These 3 subscales are summed up in the PANSS total score. b) Selective items from the NIMHANS neuropsychological battery measured cognition at baseline and end of study (12 weeks). The cognitive domains assessed were executive function, attention, planning, and memory. The battery of tests consisted of 5 subtests of Trail making tests A and B (TRAIL A and TRAIL B), Digit Vigilance Test, Auditory Verbal Learning Test (AVLT), and the Tower of London [12].

Statistical analysis

Demographic data were analyzed with descriptive statistics such as mean with SD for the continuous variables. Frequencies and percentages were provided for the Categorical variables. All analyses were based on the intention to treat sample and was performed using the Last Observation Carried Forward (LOCF) procedure [14]. The Continuous variables will be compared across the groups (Intervention *Vs.* Control Group) using an independent t-test. The dependent variables were measured at 4-time points (Baseline, 1st month, 2nd Month, and 3rd Month). The dependent variables are "Positive Symptoms", "Negative Symptoms", "General Psychopathology" and "Total Score". The over-a-period change was accessed using the Repeated Measures of ANOVA method. Mauchly's test for the sphericity assumption was violated for the above Scores ($p<0.001$). To overcome the issue of sphericity, repeated Measure ANOVA with Greenhouse-Geisser was performed. A $p<.05$ was considered statistically significant. Analysis of data was done using the Statistical Package for Social Sciences version 20 [15].

Results

Baseline patient characteristics

A total of 100 participants were recruited, of which 50 were in each intervention and placebo groups respectively. Of these 22 patients dropped out from the study, where 14 withdrew and 8 didn't follow up for endline assessments and blood investigations. Therefore 78 patients completed the study. No serious adverse events were reported in both the groups (Tables 3-6) (Flow Chart).

Table 3: Represents comparison of metabolic profiles between the intervention and placebo groups.

Effect	Estimate (95% CI)	P value
Fasting Glucose		
Time*Group	-7.68(-20.5,5.1)	0.238
Fasting Insulin		
Time*Group	-4.33(-8.5, -0.16)	0.042
C-reactive Protein (CRP)		
Time*Group	0.49(-1.63,0.65)	0.398
Cholesterol		
Time*Group	-9.30(-18.2, -0.42)	0.04
Triglycerides		
Time*Group	-8.11(-30.2,14)	0.47

The coefficient for Fasting Insulin Time*Group is -4.33, with a 95% Confidence Interval (CI) of (-8.5, -0.16) and a p-value of 0.042. This indicates a 4.33 unit's greater reduction in fasting insulin levels over time in the intervention group compared to the placebo group. The significant p-value suggests that this difference is statistically significant.

The coefficient for Cholesterol Time*Group is -9.30, with a 95% CI of (-18.2, -0.42) and a p-value of 0.040, indicating a 9.30 units greater reduction in cholesterol levels over time in the intervention group compared to the placebo group, and this difference is statistically significant.

Table 4: Represents repeated measure analysis for comparison of the intervention and placebo treatment effects on PANSS total score.

	Group	Mean	Std. Deviation	N	Test within subject effects F ratio with p value
Total Baseline	Placebo	82.2	21.439	50	F ratio (1.991,195.087) = 0.140 p value=0.868
	Intervention	82.82	17.823	50	
	Total	82.51	19.617	100	
Total 1st Month	Placebo	70.9	28.316	50	
	Intervention	70.7	23.723	50	
	Total	70.8	25.989	100	
Total 2nd Month	Placebo	53.14	28.571	50	
	Intervention	50.82	33.638	50	
	Total	51.98	31.071	100	
Total End line	Placebo	42.26	21.521	50	
	Intervention	40.34	31.384	50	
	Total	41.3	26.789	100	

The result from the above table shows that there is no significant difference in the total scores of PANSS (positive symptoms, negative symptoms, general psychopathology) between the intervention and placebo groups.

Discussion

Microbiotal composition associated with mental disorders were shown to have decreased diversity compared to the microbiome in healthy controls In general, patients with mental disorders were shown to have fewer bacterial genera that produce short-chain fatty acids (e.g. butyrate) and higher levels of lactic acid-producing bacteria, and bacteria associated with glutamate and GABA metabolism On a genus

Table 5: Represents repeated measure analysis for comparison of the intervention and placebo treatment effects on positive symptoms in PANSS.

	Group	Mean	Std. Deviation	N	Test within subject effects F ratio with p value
Positive Symptoms Baseline	Placebo	17.92	7.724	50	F ratio (1.749, 171.387) = 3.487 p value=0.039.
	Intervention	16.08	7.024	50	
	Total	17	7.403	100	
Positive Symptoms 1st Month	Placebo	16.56	7.129	50	
	Intervention	15.1	6.867	50	
	Total	15.83	7.002	100	
Positive Symptoms 2nd Month	Placebo	14.26	6.583	50	
	Intervention	14.2	6.331	50	
	Total	14.23	6.426	100	
Positive Symptoms End line	Placebo	12.08	5.685	50	
	Intervention	12.86	5.956	50	
	Total	12.47	5.806	100	

PANSS: Positive and Negative Symptoms Scale

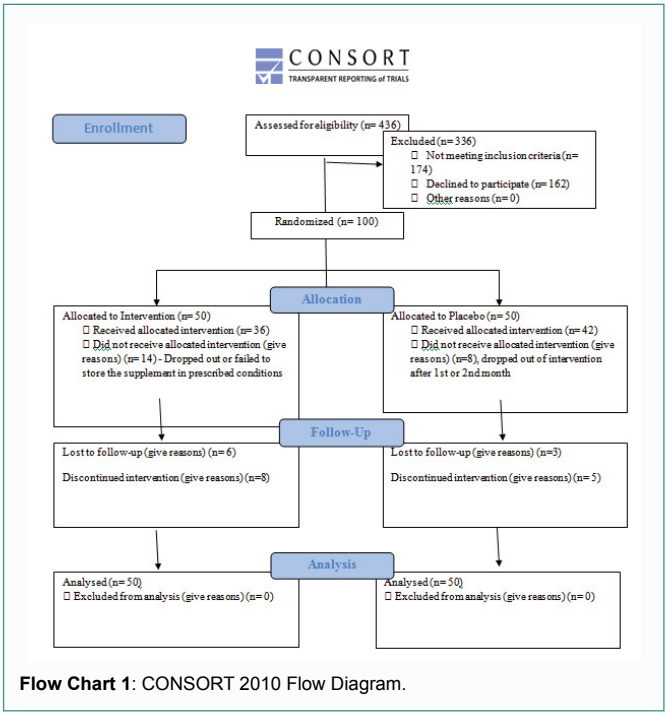
Analysis was performed using repeated measures ANOVA, as shown in Table 5, Over a period, there is a statistically significant difference in the positive symptom's domain between the intervention and placebo groups (F (1.749, 171.387) = 3.487, P = 0.039) measured at baseline, 1st & 2nd month and end line using PANSS.

Table 6: Represents the pre-post comparison between the intervention and placebo group.

	Placebo (N=50)	Intervention (N=50)	P Value
	Mean ± SD	Mean ± SD	
Trial A Baseline	88.6 ± 33.7	86.7 ± 43.9	0.748
Trial A Endline	86.6 ± 45.1	87.1 ± 42.7	
Trial B Baseline	209.9 ± 72.1	188.1 ± 82.2	0.45
Trial B Endline	206.9 ± 74.9	196.5 ± 114.5	
Digit Vigilance Time Baseline	686.9 ± 207.7	666.6 ± 214	0.71
Digit Vigilance Time Endline	700.8 ± 555.4	652.6 ± 254.8	
Digit Vigilance Error Baseline	44 ± 58.8	44 ± 58.6	0.982
Digit Vigilance Error Endline	36.8 ± 45.6	36.6 ± 53.8	
AVLT Total Baseline	39.4 ± 10.4	36.8 ± 10.3	0.976
AVLT Total Endline	44.3 ± 11.4	41.6 ± 11.3	
AVLT (LTPR) Baseline	80.6 ± 33.2	76.1 ± 26	0.843
AVLT (LTPR) Endline	85.1 ± 28.4	79.6 ± 27.5	
TOL TNPMM Baseline	8.3 ± 2.5	8.2 ± 2.3	0.514
TOL TNPMM Endline	8.7 ± 2	8.4 ± 2.3	

AVLT: Auditory Verbal Learning Test; LTPR: Long Term Percent Retention; TOL: Tower of London; TNPMM: Total Number of Problems Solved with Minimum Moves

The pre-posttest comparison did not show any significant differences in the scores of the subtests of NIMHANS neuropsychological battery that assess the cognitive functions such as attention, memory and planning ability. The results indicate mean differences between the intervention and placebo groups but there is no statistically significant difference.



Flow Chart 1: CONSORT 2010 Flow Diagram.

level, in patients with schizophrenia, Prevotella levels were higher and Bacteroides, Haemophilus, and Streptococcus were lower. Some antipsychotics and antidepressants have been shown to have antibiotic effects and this might be one reason that treatment with psychiatric medication is associated with a less diverse microbiome composition which, again, is associated with weight gain Furthermore, the proportion of some bacteria stems in the microbiome correlated with the extent of antipsychotic-induced weight gain and in in patients with antipsychotic treatment, a decrease in specific bacterial species was associated with an increase in insulin resistance [16]. Our study also generated similar findings among the participants.

Limitations and future direction

This was a double-blind, placebo-controlled, prospective study with adequate sample size. Among the patients, there existed a common challenge was adherence to the consumption of the prescribed supplement. A multicentric longitudinal study with large sample size using standard combination of the probiotic compound and with minimal confounding variables should be planned to explore the desired efficacy of the supplement in improving different cognitive domains and negative symptoms.

Conclusion

Probiotics as an adjuvant treatment for 12 weeks causes a significant change in the positive symptom psychopathology, cholesterol level and insulin resistance among Schizophrenia spectrum patients in the intervention arm. No difference in negative symptoms and cognitive domain.

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