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THE EFFECT OF PROBIOTIC SUPPLEMENTATION ON GUT MICROBIOTA COMPOSITION AND DIGESTIVE HEALTH IN HEALTHY ADULTS

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Abstract

Background: *The GIT houses a diverse colonies of mutualistic or beneficial bacteria such as Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobia phyla. Probiotics are commonly used to support such organisms and promote gut health but the evidence regarding their effectiveness in healthy locals as lacking. Gut microbiota can depend on the dietary patterns and lifestyles which makes it important to assess its effect in regional context. The aim of this study was to investigate whether probiotic supplementation can improve gut microbiota and digestive health among healthy adults.* ***Methods:*** *A randomized control trial with a sample of 46 healthy adults recruited from outpatient department of General Hospital Lahore, Pakistan. Purposive sampling technique was used. After screening for eligibity criteria and obtaining an informed consent, the participants were assigned to either probiotic group (Group A) or placebo group (Group B) using lottery ticket method of randomization. Gut microbiota composition was assessed by Dysbiosis Index (DI), stool samples were collected using sterile collection kits which contained DHA stabilizing preservative at baseline and at the 12th week of intervention. Digestive health was assessed by Gastrointestinal Symptom Rating Scale (GSRS). Analysis was performed by SPSS version 26. The data was normally distributed, the in-group comparisons were analyzed by Paired Sample T-test and the between group comparisons were done by Independent Sample T-test.* ***Results:*** *The Independent sample T-test analysis showed that that there was a statistically significant difference between the baseline and 12th week Dysbiosis Index between group A and group B ($p < 0.001$) and similarly the baseline and 12th week GSRS score between group A and group B was found to be statistically significant ($p < 0.001$).* ***Conclusion:*** *The probiotics supplementation has a significant effect of gut microbiota composition and digestive health. The gut microbiota balance was found to be improved after the 12-week probiotic supplementation in group A and it also contributed to a better digestive health.*

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INTRODUCTION

A large community of microorganisms reside in and on the human body. In addition to that, the gastrointestinal tract (GIT) houses a variety of and dynamic colony of mutualistic or beneficial bacteria mainly Bacteroidetes, Firmicutes, Proteobacteria and Verrucomicrobia phyla. [1] The GIT load ranges from 10^{12} CFU per milliliter in the month and a thin variation of 10^{7} CFU per milliliter in the stomach and duodenum and an enormous variation of 10^{14} CFU per milliliter in large intestine. [2] The upper GIT is home to Gram-positive cocci such as *Streptococcus* and *Gemella*, as the concentration of oxygen is low along the longitudinal axis of the GIT. On the other hand, the intestine and colon are a home to vast communities of anaerobes that include *Clostridium* and *Faecalibacterium* genera. [3] In addition, the organization of the bacteria is based on the ability for the degradation of mucus in the luminal to mucosal axis. The microbe mainly present in the mucosal layer that use glycans as a means fuel source by glycosidase, sulphatase, and sialidase enzymes. [4] The depletion of dietary fiber polysaccharides highlights the significance importance of host intestinal mucin as a dependable fuel source for gut microbiota, considering the dynamic colonization of native microbes inside the intestines produced by the glycans. [5]

The ability of the intestinal immune system to differentiate between pathogens and mutualistic germs and to develop active resistance towards commensal bacteria is an exceptional trait. [6] Various cellular signaling pathways are activated when receptors for pattern recognition, such as toll-like receptors and nucleotide-binding oligomerization domain receptors, recognize microbe-associated molecular patterns. Hence, the levels of inflammatory cytokines, chemokines, and immunoreceptors produced can be altered by the manipulation of gene expression by different ligands, transcription factors, and kinases. [7] Several processes are taken into account in TLR-mediated differentiation of gut bacteria, including the fact that pathogens and beneficial bacteria share ligands that engage the TLRs. Because commensals and pathogens range in invasiveness and lack virulence factors, these can be simply distinguished from one another. Additionally, these beneficial bacteria are unable to access the cell site of TLRs on the epithelium of the intestine. Other possible approaches for differentiating bacteria from infections causing include stimulating ligand-specific signaling cascades and distinct PAMP selectivity for TLRs. [8] Conversely, NOD2 identifies conserved patterns of bacterial peptidoglycan and preserves the functionality of the mucus layer; hence, NOD2 loss or mutation may result in pathogen growth, swelling, and colon cancer. [9] According to a recent evidence, NOD2 deletion mice exhibited an inadequate healing of gut microbiota balance after an antibiotic intervention, indicating this receptor's significant role in constructing the gut microbial community. Additionally, activation of the NOD1 based on peptidoglycan recognition can cause tolerance and immunological memory. [10] Moreover, immunological memory and tolerance can be promoted by NOD1 activation which occurs from peptidoglycan identification. Irving et al. showed that H. pylori infection causes particular peptidoglycan immunity, which is followed by the activation and induction of NOD1 and autophagy respectively. [11]

By generating an anti-inflammatory response in dendritic cells (DCs), the intestinal epithelium mucosal layer serves as a static shield among the resident microbiota and the epithelial layer in turn lowering the immunogenicity of antigens. Furthermore, intricate architecture of the intestinal epithelium and secretions, including immunoglobulins and antimicrobial peptides (AMPs), preserving the integrity of mucosal barriers. [12] Defensins, which create pores in bacterial membranes to compromise the integrity of cell, are the most prevalent AMPs. The two groups of defensins which

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are α- and β-defensins, are mostly secreted by colonic epithelial cells and Paneth cells, respectively. [13] These AMPs are able to entrap bacteria as they create an extracellular net like formations and degenerating the bacterial cytoplasm in addition to creating pores. [14] Additionally, irrespective of the presence of bacteria, cathelicidin is the main AMP expressed throughout infancy and has a significant impact on the initial development of gut microbiota. [15] Both preterm and term newborns may exhibit long-term immunological and metabolic problems if their gut flora is disrupted. [16] Together, the intestinal epithelium can create immunological tolerance against commensal bacteria and an effective barrier of physico-chemicals that intercepts the colonization of pathogen on the mucosal surface.

Recent studies have shown that the adaptive immune system interacts mutually with the immune system if an infant to shape the makeup of gut microbes. B lymphocytes is crucial in regulating intestinal homeostasis, primarily by producing secretory immunoglobulin A (SIgA) in reaction to mutualistic detection. [17] The gut microbial ecology is essential to SIgA's crucial and frequently oversimplified function. SIgA's disorderly or excessive response to changes in the diversity or proinflammatory activities of certain strains affects not just the individual bacteria but most likely the entire microbiota. [18] SIgA primarily inhibits conjugative plasmid transfer, stops microorganisms from moving from the lamina propria to the circulation, and promotes commensal bacterial colonization. [19] T follicular helper cells, on the other hand, are specifically designed to work with B cells and alter the B cell mediated immunity. [20] It is still to this day not fully understood the way an immune system that is adaptive shapes the gut microbiota, despite a number of research starting to clarify the molecular relationship between cellular immunity and gut microbiota through inflammatory signaling pathways.

Through metabolites derived from the gut microbiota, particularly bile acids, short-chain fatty acids, branched-chain amino acids, trimethylamine N-oxide, tryptophan, and derivatives of indole, the gut microbiota plays a crucial part in maintaining the host's normal biological acitivity. [21] Although little is known about how the gut microbiota directly affects human metabolism, the gastrointestinal microbiota and mitochondria have a unique relationship because of their shared ancestry. [22] Recent data on the matter shows that the production of deltavalerobetaine in microbiome of the gut lowers carnitine in cells and mitochondrial long chain acyl-coenzyme A (acyl-CoA); as a result, this obesity inducing molecule blocks oxidation of mitochondrial fatty acid and causes obesity that is dependent on diet. [23]

Saturated fatty acids (SCFAs) are majorly found in the human body as acetate (C2), propionate (C3), butyrate (C4), and valeric acid (C5). They are obtained from microbiota-accessible carbohydrates. [24, 25] However, the gastrointestinal transit duration, gut microbiota type, and substrate availability all affect the amount of each SCFA. As their potency rises from the distal ileum to the proximal colon, SCFAs show a number of local actions, including maintaining the integrity of the barrier of intestine and lowering pH. [26, 27] Additionally, SCFAs inhibit pathogen-induced inflammation, generate and grow intestinal regulatory T cells, [28] DCs, and macrophages, [29] and have anticarcinogenic and anti-oxidative effects in the gut. [30, 31]

Hepatocytes produce main bile acids, combine them to taurine or glycine, and then emit them into the gall bladder to create bile together with protein, phospholipids, minerals, electrolytes, bilirubin, and biliverdin. [32] Primary BAs that are not reabsorbed in the terminal ileum will be deconjugated by intestinal bacteria and transformed into secondary BAs through microbial biotransformation, which includes hydroxyl group oxidation, dehydroxylation, and epimerization. [33] The host immune response, intestinal metabolism, microbial composition, and cell signaling are all influenced by secondary BAs. IBS and IBD,

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such as Crohn's disease (CD) and ulcerative colitis (UC), are linked to decreased BA deconjugation. While conjugated BAs like glycolic acid, glycodeoxycholic acid, and glycochenodeoxycholic acid stimulate cell proliferation and increase the synthesis of interleukin 6 (IL-6), free BAs like cholic acid, deoxycholic acid, and chenodeoxycholic acid can increase apoptosis and decrease IL-6 production. [34] However, overproduction of the secondary BA deoxycholic acid causes hepatic stellate cells (HSCs) to produce inflammatory and carcinogenic markers, which aids in the development of hepatocellular carcinoma. Fifty Additionally, secondary BAs may activate the farnesoid X receptor, increasing the chances of hepatocellular carcinoma and colorectal cancer. [35]

To assert intestinal dysbiosis and find disease-related biomarkers, the make-up and function of the gut microbiota in metabolically healthy individuals must be defined. The host-microbiota interaction presents a tremendous amount of complexity that requires extensive, multidisciplinary approaches for further clarification. [36] While the composition of a healthy microbiome is still unknown, the relative change of gastrointestinal microbes in illness to assert intestinal dysbiosis and find disease-related biomarkers, it is necessary to define the make-up and function of the gut microbiota in metabolically healthy individuals. [37]

The probiotics are widely recognized as a means to improve digestion and gut health; however, no solid evidence is found when it comes to local population especially beginning with finding its effects on healthy adults. The gut microbiota can be altered by changes in factors such as regional diet, lifestyle, and the exposure of antibiotics which highlights the need for evaluating the effect of probiotics in local context rather than relying on the data that is available internationally. This RCT aims to provide population specific evidence on the effects of probiotic supplementation in order to present measurable results that assess the improvements in gut microbiota and digestive health. The findings of this study are also going to be beneficial for clinicians helping them make evidence-based assessments and recommendations and to reduce the unnecessary reliance on commercial claims that can be unverified, it will also act like a meaningful data guide for the future research and clinical decision-making.

Methods

A randomized control trial was performed and the sample included 50 healthy adult participants aged 18 to 50 years residing in Lahore, Pakistan. The participants were recruited from the outpatient department of Lahore General Hospital. Purposive sampling technique was used to identify the eligible participants. The eligibity criteria included subjects with no history of gastrointestinal disorders such as celiac disease, IBS, IBD, subjects who are currently not taking any probiotics, prebiotics or antibiotics and have not taken in the past 8 weeks, subjects who were willing to provide stool sample at baseline and at 12th week, and subjects with no significant comorbidities what could affect the gut microbiota or digestive health such as liver disease, fatty liver or uncontrolled diabetes. Subjects using antibiotics, probiotics or prebiotics, history of gastrointestinal surgery, any gastrointestinal diseases, any known allergies or intolerances to probiotic formula, severe systematic illness, pregnant or lactating women, inability/unwillingness to comply with study procedures such as stool collection were excluded.

After screening for eligibity criteria and obtaining an informed consent, the participants were designated to either probiotic group (Group A) or placebo group (Group B) using lottery ticket method of randomization. The study was single blinded as the participants were blind and the assessor and researcher were not. The participants completed a demographic form that included info regarding age, gender, Gut microbiota composition was assessed by Dysbiosis Index (DI), stool samples were collected using sterile collection kits which

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contained DHA stabilizing preservative at baseline and at the 12th week of intervention. Participants were instructed regarding proper collection of the stool sample, labelling the sample with the group of the participant, date and time. The samples were then transferred to Molecular Diagnostics Laboratory in Lahore, Cantt for the purpose of microbial DNA extraction and bacteria profiling by 16S rRNA gene sequencing. A Dysbiosis Index (0-10) was generated for each subject with lower score indicating a balanced microbiota and higher score indicating grater dysbiosis. Digestive health was assessed by Gastrointestinal Symptom Rating Scale (GSRS).

Participants in Group A took a multi-strain probiotic capsule once a day for 12 weeks after breakfast which contained Lactobacillus rhamnosus, Lactobacillus acidophilus, and Bifidobacterium bifidum at a 10° CFU total concentration. Group B participants received an identical looking capsule containing maltodextrin at an inert state with none of the bacterial cultures that were active. The participants were instructed to the capsule once a day and avoid using any other OTC medicines or supplements during the intervention period.

Statistical Analysis

The data was statistically analyzed using SPSS version 25. The continuous variables were presented as mean and standard deviation whereas categorical variables were presented as frequency and percentages. The changes in outcome measures from baseline to 12th week were compared between group A and group B using statistical tests to calculate inferential statistics. As the data showed a normally distribution, the in-group comparisons were analyzed by Paired Sample T-test and the between group comparisons were done by Independent Sample T-test.

RESULTS

Out of 50 participants, 46 completed the trial, while 2 participants from group A and 2 participants from group B withdrew from the study. The data of this study was normally distributed as analyzed by Shapiro-wilk test. The average age of the participants in group A was 37.26 ± 7.26 years and in group B was 34.74 ± 7.98 years. Out of 23 participants in group A, 7 (30.4%) were male and 16 (69.6%) were female. In group B, 9 (39.1%) were female and 14 (60.9%) were male. The Dysbiosis Index at baseline was 5.19 ± 2.04 in group A and 4.79 ± 2.06 in group B. At 12th week, the Dysbiosis Index was 3.78 ± 2.07 in group A and 4.49 ± 1.56 in group B. The GSRS baseline score was 3.43 ± 0.80 in group A and 3.77 ± 1.19 in group B, At 12th week the GSRS score was 2.84 ± 0.90 for group A and 3.59 ± 1.17 for group B. The in-group comparison of baseline and 12th week score of Dysbiosis Index was found to be significant ($p < 0.001$) among group A and the baseline and 12th week score of GSRS for this group was also significant ($p = 0.006$). For group B the baseline and 12th week score of Dysbiosis Index was found to be not statistically significant ($p = 0.097$) and the baseline and 12th week score of GSRS was also found to be not statistically significant ($p = 0.193$). The between group comparisons revealed that there were significant differences among the baseline and 12th week Dysbiosis Index between group A and group B ($p < 0.001$) and similarly the baseline and 12th week GSRS score amongst group A and group B were found to be statistically significant ($p < 0.001$).

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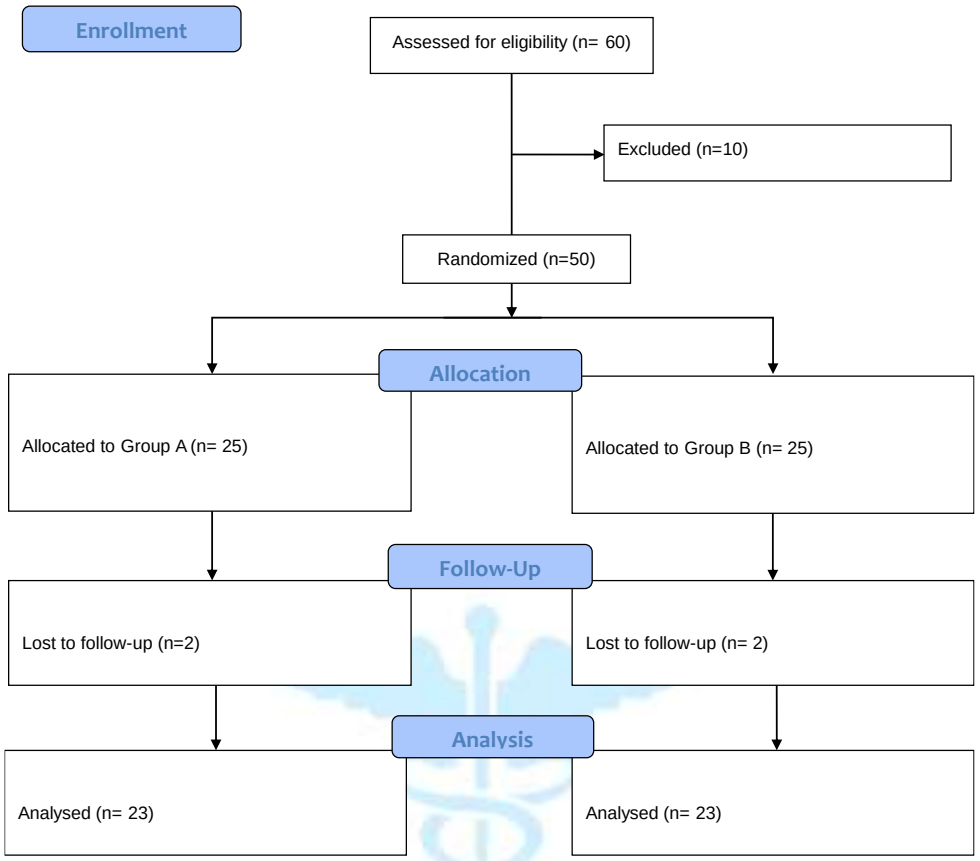

Figure 1: Participant Enrollment Flowchart

DISCUSSION

This randomized control trial including the population of healthy adults revealed that probiotic supplementation (Group A) can significantly improve both the gut microbiota composition as measured by Dysbiosis Index and the digestive health as measured by the Gastrointestinal Symptom Rating Scale, GSRS over a period of 12 weeks when compared to the placebo (Group B). A reduction in the Dysbiosis Index was noted from 5.19 ± 2.04 to 3.78 ± 2.07 ($p < 0.001$) and this reduction was also observed in the Gastrointestinal Symptom Rating Scale score as well from 3.43 ± 0.80 to 2.84 ± 0.90 ($p = 0.006$) in group A whereas in group B these scores showed no statically significant changes. The between group differences were highly significant (p , 0.001) for both of the indices. These findings suggest that the probiotic supplementation may be beneficial to modulate the gut microbial balance and the subjective digestive health among genialized healthy adult population.

Comparing these finding to the literature available prior, both divergence and concordance emerge. On the other hand, the concept that probiotics improve gastrointestinal function in healthy adults is supported by recent body of research. A post-hoc analysis of a 12-week randomized control trial, double blinded placebo-controlled study performed in healthy adults revealed a reduction in the overall daily gastrointestinal complains which included bloating, stomach pain, borborygmic, incomplete defecation in a group that was treated with probiotics when compared to the placebo. They also noted slight shifts in the gut microbiota composition and the inflammatory markers, the results of this trial align with the findings of current study. [38] Similarly, an open label study of multi-strain

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probiotic with the population of healthy adults performed for 8 weeks showed an increase in beneficial taxa which included *Lactobacillus, Akkermansia muciniphila, and Faecalibacterium prausnitzii* in the stool sample without any adverse effects. [39] These findings and observations align with the results of current RCT as it displayed an improved dysbiosis and symptomatic score supporting the notion that probiotic interventions contribute to improved gut health among healthy adults.

A skeptical perspective is offered by systematic review, a review of randomized control trials of up to 2015 concluded that the probiotic supplementation among healthy adults is found to rarely produce any consistent changes in the fecal microbiota composition. Only one of the all seven randomized control trials showed that there is a change in the overall community structure when compared to the placebo group. [40] An uncertainty is echoed by the recent reviews as an updated systematic review published in 2021 included eight randomized control trials, highlighted the substantial heterogeneity in strains, durations, doses, and outcome measures which underscores the data available remains insufficient to provide a long-term and stable effect on gut microbiota of healthy adults. [41] Similar to this, a control trial which utilized a single probiotic strain of Bacillus coagulans MTCC 5856 failed to cause any major shifts in the gut microbiome composition, however it confirmed the safety and tolerability of the supplementation. [42]

In terms of limitations, the sample size of the study is modest, although sufficient to detect clear in and between group comparisons, larger sample sizes would offer increased robustness as will as allow for subgroup analysis such as by gender, diet, dysbiosis severity etc. Also, without a follow-up after the cessation of supplementation, the effect on the gut microbiota still remains unclear whether the improvements will persist, revert or evolve. Future researched are advised to include a follow-up period after the cessation of supplementations to look into the post-supplementation effects. In addition to that, future researchers can compare the effect that different probiotic strains, their dosages, the duration can have as this would aid in establishing the optimal regimens for the maintenance of gut health, microbiota and overall digestive health among healthy adults.

CONCLUSION

This RCT provided a locally relevant evidence on the effect of probiotics supplementation in healthy adults. The findings of this study show that probiotic supplementation lead to improvement in the gut microbiota composition balance which was reflected by a reduced mean score of Dysbiosis Index after the 12 weeks. It also contributed to better digestive health as the GSRS score was improved when compared to the placebo. These results highlight and support the use of probiotics for maintaining gut health among healthy individuals.

Conflict of Interest

The authors declare that there are no conflicts of interest relevant to this study

Table 1 Demographic characteristic of participants in the two groups

Characteristics		Group A (Probiotics) (n = 23)	Group B (Placebo) (n = 23)
Gender	Male	7 (30.4%)	14 (60.9%)
	Female	16 (69.6%)	9 (39.1%)
Age		37.26 ± 7.26	34.74 ± 7.98
BMI		24.49 ± 3.05	23.64 ± 2.29

Table 2 Study Variables at baseline and 12th week

Variable	Group A (Probiotics) (n = 23)	Group B (Placebo) (n = 23)

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Dysbiosis Index (baseline)		5.19 ± 2.04	4.79 ± 2.06
	Moderate Dysbiosis	16 (69.6%)	14 (60.9%)
	Normal	3 (13%)	6 (26.1%)
	Severe Dysbiosis	4 (17.4%)	3 (13%)
Dysbiosis Index (12th week)		3.78 ± 2.07	4.49 ± 1.56
	Moderate Dysbiosis	13 (56.5%)	19 (82.6%)
	Normal	9 (39.1%)	4 (17.4%)
	Severe Dysbiosis	1 (4.3%)	-
GSRS (baseline)		3.43 ± 0.80	3.77 ± 1.19
	Mild Symptoms	7 (30.4%)	5 (21.7%)
	Moderate Symptoms	16 (69.6%)	16 (69.6%)
	Severe Symptoms	-	2 (8.7%)
GSRS (12th week)		2.84 ± 0.90	3.59 ± 1.17
	Mild Symptoms	14 (60.9%)	6 (26.1%)
	Moderate Symptoms	9 (39.1%)	16 (69.6%)
	Severe Symptoms	-	1 (4.3%)

Table 3 In group paired sample T-test analysis of study variables at baseline and 12th week

Group	Variable	M	S. D	t-value	df	P-value
Group A	Dysbiosis Index	1.41	0.61	11.11	22	0.001
	GSRS	0.59	0.93	3.03	22	0.006
Group B	Dysbiosis Index	0.30	0.83	1.73	22	0.097
	GSRS	0.17	0.61	1.34	22	0.193

Table 4 Between group Independent sample T-test analysis of study variables after intervention

Variable	M	S. E	t-value	df	P-value
Dysbiosis Index	1.11	0.21	5.18	44	0.001
GSRS	0.84	0.22	3.82	40.83	0.001

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