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Review

INFLUENCE OF PROBIOTIC SUPPLEMENTATION ON NUTRIENT ASSIMILATION IN HEALTHY PEDIATRIC POPULATIONS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EXPLORATORY STUDY

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ABSTRACT

The rise in global use of dietary supplements, especially probiotics, necessitates assessing their effectiveness. Probiotics, beneficial microorganisms like lactic acid bacteria, improve health by modifying the gut microbiota. They are effective in treating gastrointestinal and allergy disorders, obesity, diabetes, and boosting immunity. This study evaluates the impact of a specific probiotic formulation on children's health and nutrient absorption. In a randomized, double-blind, placebo-controlled trial, 40 pediatric patients aged 14 to 18 were divided into active treatment and placebo groups. The active group received Hyperbiotics PRO-Kids, a symbiotic containing four proprietary probiotic strains and a prebiotic. Clinical outcomes, including blood levels of vitamins, calcium, iron, and zinc, were monitored over 10 weeks. The probiotic group showed significant improvements in weight, BMI, and nutrient absorption, with no adverse effects reported, suggesting probiotics enhance children's immune and nutritional health. However, further research is needed due to limitations like the small sample size and lack of fecal microbiota analysis. Future studies should focus on understanding probiotics' mechanisms and optimizing protocols for pediatric use, emphasizing the need for customized probiotic delivery and recognizing the variability in strain efficacy.

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INTRODUCTION

The use of dietary supplements, such as probiotics, has increased globally. Probiotics, derived from the Greek term meaning "for life," are non-pathogenic organisms (yeast or bacteria, particularly lactic acid bacteria) in foods that positively influence health. Modulating the gut microbiota can involve using probiotics, indigestible carbohydrates (prebiotics), or combinations of both (symbiotic) (1,2).

Clinical studies have shown that probiotics positively affect gastrointestinal diseases (like irritable bowel syndrome, Helicobacter elimination, inflammatory bowel disease, and diarrheas) and allergic diseases (such as atopic dermatitis) (3–5). Probiotics have also been effective in treating obesity, insulin resistance syndrome, type 2 diabetes, and non-alcoholic fatty liver disease, and in enhancing immunity (6). Probiotics and prebiotics have been shown to enhance nutritional status by reducing gastrointestinal disorders and to enhance the absorption of micronutrients (such as iron and calcium) from diet (7,8). The primary bacterial stimulation of gut-associated immune cells is crucial for developing and maturing the immune response in children. However, this has been impacted by fewer vaginal births, less breastfeeding, increased use of antibiotics, and more stringent hygiene and pasteurization practices (9–11).

Consuming certain probiotics benefits gut barrier function and immune response, enhancing host-microbe interactions, nutrient harvesting, and production of substances like short-chain fatty acids, vitamins, amino acids, polyamines, growth factors, and antioxidants (Fig.1). This helps manage various illnesses (12–14).

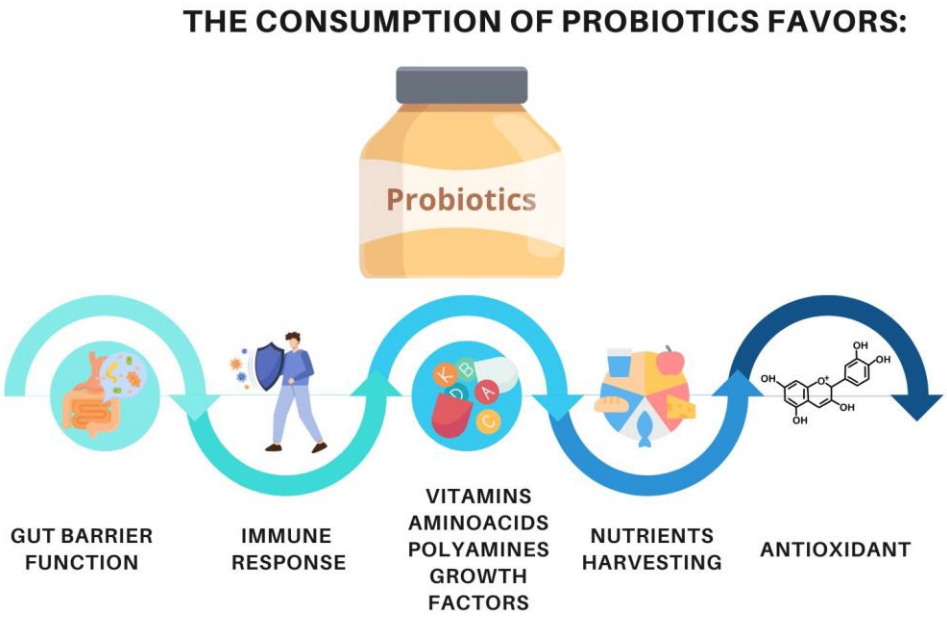

Fig. 1. *The consumption of probiotics favors gut barrier function, immune responses, vitamins, aminoacids, polyamines, growth factors, nutrients harvesting, and antioxidants.*

Current studies focus on understanding the in vivo mechanisms and challenges in translational research on probiotics (15). The application of immunological tests for probiotic selection may become clearer with a deeper understanding of the clinical and molecular mechanisms of probiotics, the effects of probiotic mixes vs single strains, probiotic composition, and the destiny of ingested probiotics (16–18).

This translational study aims to evaluate the efficiency of specific probiotics customized for children to improve nutritional absorption and enhance overall health and immunity.

MATERIALS AND METHODS

This study, titled "Probiotics Efficacy and Safety in Humans," was a collaborative effort between Elbasan University in Albania and the University of Bari Aldo Moro. Conducted as a randomized, double-blinded, placebo-controlled trial,

it received approval from the Institutional Ethics Committee of the Faculty of Technical Medical Sciences of Elbasan. The protocol identification was INTL_ALITCOOP/Probiotics/INRES2019_w/a/c.

Subjects Recruited

A total of 40 pediatric patients, aged between 14 and 18 years, were enrolled in the study and divided into two groups (Fig.2). Prior to participation, all patients' parents or guardians were required to read, understand, and sign an informed consent form, in accordance with the ethical principles outlined in the Helsinki Declaration. The clinical protocol was verbally explained to the parents or guardians of the patients. Eligible participants were randomly assigned to either a placebo group (n = 20) or an active treatment group (n = 20), ensuring that the allocation remained blinded to the investigators (Figure 2). The study involved healthy pediatric patients with similar body mass index (BMI) and age, who were randomly assigned to receive either a placebo or a symbiotic containing a specific probiotic formulation (Hyperbiotics PRO-Kids). This formulation consisted of four patented probiotic strains (Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacter infantis, Bifidobacter lactis), along with a prebiotic (fructo-oligosaccharides), and was manufactured using the LiveBac® process and BIO-tract® technology for protection and time-release delivery. 3 billion colony-forming units (CFUs) per BIO-tract® pearl were present in the studied recipe, which is equal to 45 billion CFUs of conventional probiotic capsules. The main inclusion criteria were healthy individuals with similar BMI and age, while exclusion criteria included recent antibiotic or drug use, malnutrition, or use of nutritional supplements (19).

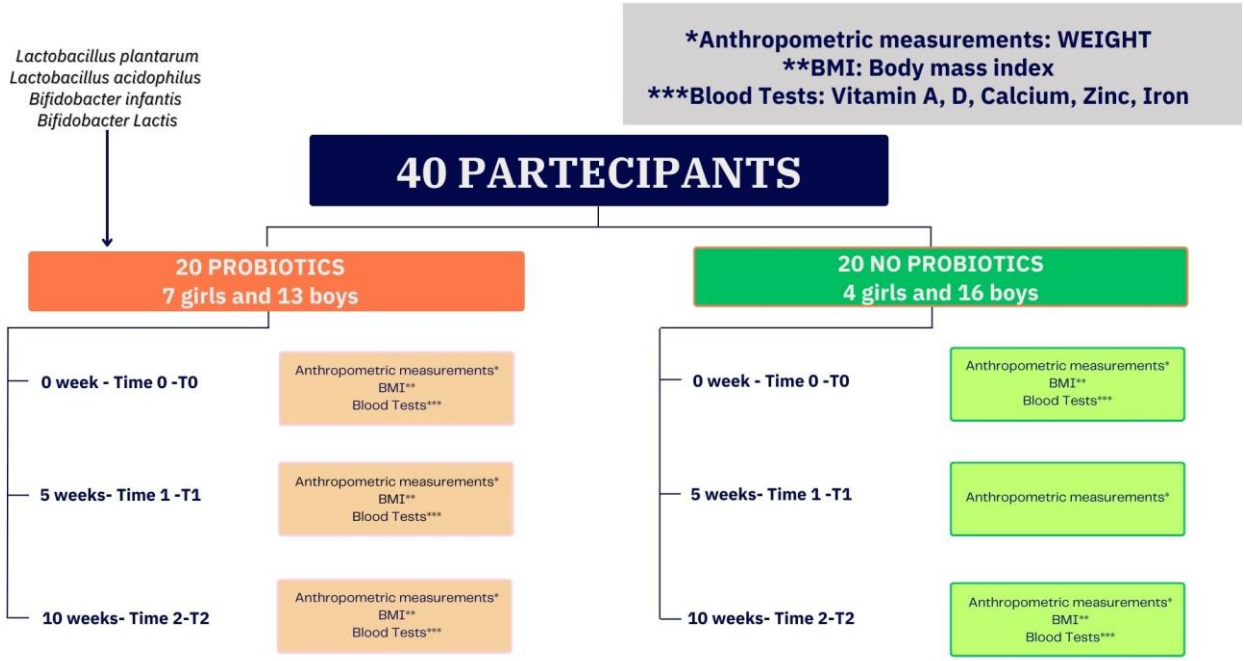

Fig. 2. *Participants in the study.*

Randomization

Enrolling patients and classifying treatments were done using a double-blind procedure to guarantee objective and reliable clinical data. Envelopes with sequential numbers were made using a computer-generated list of random numbers, and inside were assignments to receive probiotics or a placebo. The immunologist investigator oversaw the distribution of blinded supplements, whilst the clinical biochemistry investigator was in charge of randomization in the study. The supplements were the same save for their letter A or B labels. Participants, investigators, outcome assessors, and data analysts were all blinded to treatment allocations once they were assigned to interventions.

Clinical Outcomes

The primary objective of the study was to evaluate the impact of supplementing digestive probiotics, specifically Hyperbiotics PRO-Kids, on enhancing the nutritional absorption capacity in children, thereby promoting overall health and immunity. Secondary outcomes included assessing the levels of blood biomarkers such as Vitamins D and A, Calcium, and mineral absorption (iron and zinc) over a 10-week period. Blood samples were collected from participants via vein puncture, with approximately 5 ml of blood collected during laboratory sampling between 7:00 and 9:00 am.

These blood samples were then centrifuged at 2500×g for 10 minutes, and the serum was separated for serum biochemical analysis (20).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) and GraphPad Prism (version 6.01, La Jolla, CA, USA) were used to analyze the mean values for the Treaded and Control groups software (Inc., Version 16.0, Chicago, IL, USA).

The Statistical Product and Service Solution (SPSS) Statistics 21 program (IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses. ANOVA tests were used to analyze data.

A significance level of $p<0.05$ was deemed to be statistically significant.

RESULTS

This study aimed to assess the efficacy of specific probiotics tailored for pediatric use in enhancing nutritional absorption capacity among adolescents aged 14 to 18 years. The research, conducted as a randomized clinical trial, involved collaboration between Elbasan University in Albania and the University of Bari Aldo Moro. Approval from the Institutional Ethics Committee was obtained, and the study adhered to the Helsinki Declaration's ethical principles.

Forty pediatric patients were enrolled, with parents or guardians providing informed consent. Participants were randomly assigned to either a probiotic (n = 20) or placebo (n = 20) group. The probiotic used, Hyperbiotics PRO-Kids, contained patented strains of Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacter infantis, and Bifidobacter lactis, along with prebiotic fructo-oligosaccharides (FOS) and patented delivery mechanisms.

Criteria for inclusion encompassed healthy individuals with similar body mass index (BMI) and age, while exclusion criteria included recent antibiotic use, malnutrition, and active drug treatments. Randomization ensured unbiased allocation to treatment groups.

Clinical outcomes focused on assessing nutritional absorption capacity through blood biomarker levels of Vitamin D, Vitamin A, calcium, iron, and zinc at baseline (T0) and 10 weeks (T2). Statistical analysis involved comparing mean values between treatment and control groups using ANOVA tests (21,22) (Table I).

Table I. *Table showing how the Active/Treated (A) and Placebo (B) groups compare: weight increase, BMI, Vitamin D, Vitamin A, Calcium, Zinc, and Iron measured at baseline (T0) and ten weeks (T2) after probiotic/placebo administration. These results indicate that probiotic supplementation led to significant improvements in several nutritional biomarkers compared to the placebo group.*

Parameter	Treated group (T0-T2) (probiotic)	Placebo group (T0-T2)	p-value
Weight increase	+1.5%	+1.5%	<0.001
BMI	Unchanged	Unchanged	<0.001
Vitamin A	+9%	+1%	<0.001
Vitamin D	+3.2%	-3%	<0.001
Calcium	+4%	-7%	<0.001
Zinc	+1.7%	-3.5%	<0.001
Iron	+2%	-1%	<0.001

Results revealed significant differences between the probiotic and placebo groups, indicating the probiotics' positive impact. Patients receiving probiotics demonstrated improvements in weight, BMI, and blood biomarker levels compared to those in the placebo group. Notably, no adverse events were reported during the study (Fig.3,4).

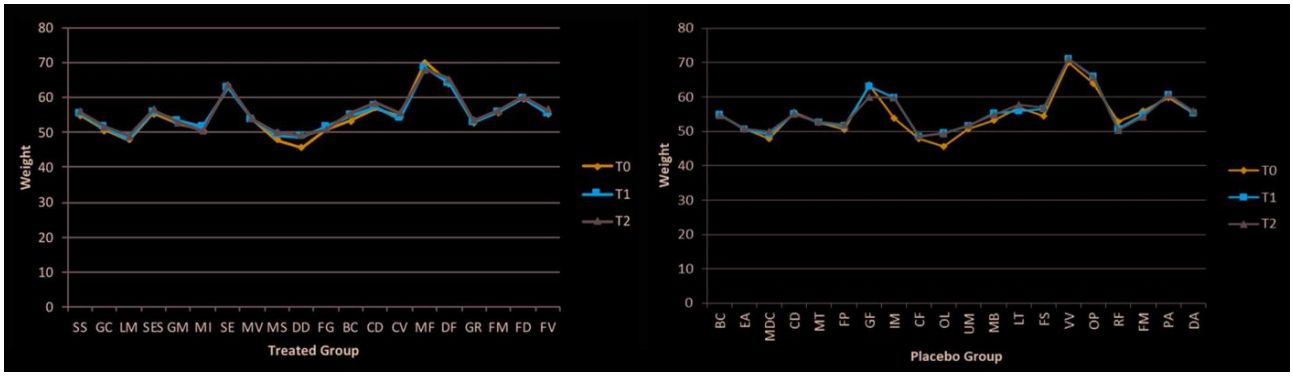

Fig. 3. *Charts show how the Active/Treated (A) and Placebo (B) groups compare: Anthropometric measurements, or body weight, were taken at baseline (T0), five weeks (T1), and ten weeks (T2) following probiotic/placebo administration. These data are of nutritional importance. The abscissa axis displayed the patient's initials (full name, family name), while the ordinate axis displayed the body weight value as the consequence.*

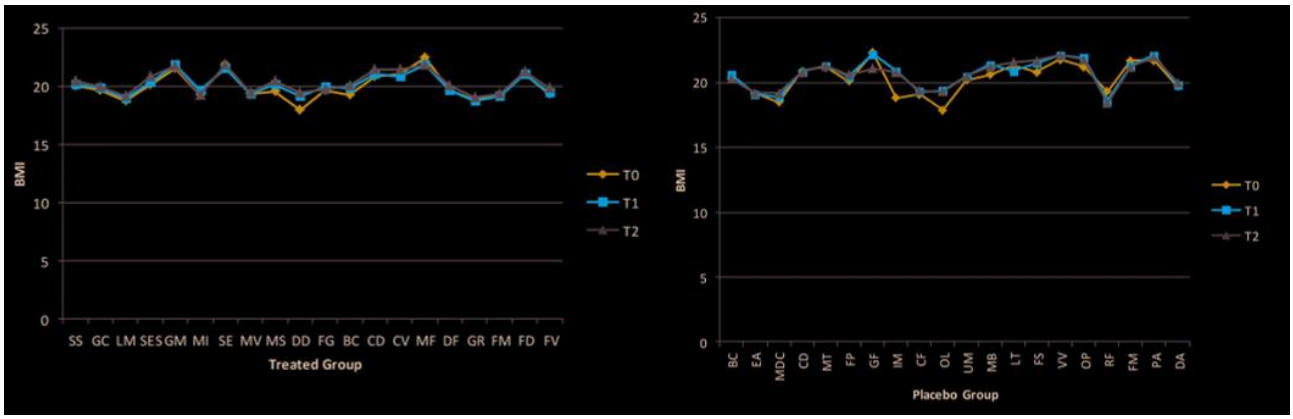

Fig. 4. *Charts show how the Active/Treated (A) and Placebo (B) groups compare: Body mass index (BMI) and other nutritionally significant data were measured at baseline (T0), five weeks (T1), and ten weeks (T2) after probiotic/placebo administration. The patient's initials (full name, family name) were given in the abscissa axis, and the outcome (BMI) value was reported in the ordinate axis.*

Discussion of previous literature highlighted the varying efficacy of probiotics in managing conditions like antibiotic-associated diarrhea (AAD) in children. Studies demonstrated mixed outcomes, emphasizing the importance of selecting appropriate probiotic strains tailored to desired clinical outcomes (23–25).

Despite limitations, including a small sample size and lack of fecal microbiome analysis, the study underscores the potential benefits of probiotics in enhancing nutritional absorption in pediatric populations. Further research is warranted to elucidate probiotics' mechanisms and optimize treatment protocols for pediatric patients (26–28).

DISCUSSION

The meta-analysis conducted in 2015 encompassed 23 studies up to 2014, evaluating the efficacy and safety of probiotics in preventing antibiotic-associated diarrhea (AAD) in pediatric populations. These studies examined various probiotic strains, including Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., and others, administered in different doses and durations. The majority of these studies reported improvements in the average duration of diarrhea with probiotic treatment, especially when administered concurrently with antibiotics. Notably, serious side effects were not observed, though minor adverse events like skin rash, vomiting, and phlegm were reported in some cases (29–32).

An earlier study from 2002 demonstrated the efficacy of probiotics in reducing the frequency of diarrhea in children (32). However, subsequent research, such as the 2018 study, found that Lactobacillus reuteri did not prevent diarrhea in children taking antibiotics. This underscores the variability in the effectiveness of different probiotic strains in this context (33–36).

In 2015, a study compared five different probiotics and found that not all were effective against antibiotic-induced diarrhea. Lactobacillus rhamnosus GG showed promise in reducing the duration of diarrhea, while Streptococcus faecium SF68 improved clinical outcomes in children with diarrhea associated with respiratory infections (23,37,38).

Further investigations evaluated probiotic yogurt containing Lactobacillus rhamnosus GG, Bifidobacterium lactis, and Lactobacillus acidophilus. This yogurt demonstrated a reduction in both the incidence and severity of diarrhea caused by antibiotics in children compared to a placebo yogurt (4,39,40).

The combination of Bifidobacterium lactis and Streptococcus thermophilus also exhibited positive effects in decreasing the frequency of diarrhea in children undergoing various antibiotic treatments (3,41–43).

The rationale behind using probiotics to mitigate antibiotic-induced diarrhea lies in their ability to restore the balance of intestinal microbiota disrupted by antibiotics. However, not all probiotic strains exhibit equal efficacy, and the parameters used to evaluate their effectiveness vary among studies. Some strains, such as LGG and S. boulardii, have consistently shown efficacy in reducing the risk of antibiotic-associated diarrhea in children (1,44–46).

Despite these findings, certain limitations need to be considered, including the variability of the intestinal microbiota among individuals and the absence of fecal microbiome analysis in some studies. Overall, while certain probiotic strains hold promise in preventing antibiotic-associated diarrhea in children, further research is necessary to refine recommendations and gain a comprehensive understanding of their mechanisms of action (31,32,47).

Moreover, recent studies have focused on exploring different types of probiotics and their efficacy in preventing antibiotic-associated diarrhea. For example, a study in 2018, still ongoing, is testing various probiotics in children undergoing antibiotic treatment. This study aims to evaluate the consistency and frequency of stools daily, both during and after antibiotic use, to assess the effectiveness of probiotics in preventing diarrhea (34,37,48).

Articles addressing the prevention and treatment of diarrhea caused by antibiotic use are increasing. In 2017, guidelines were established for the combined use of probiotics with antibiotics to prevent diarrhea in children. This systematic review identified two probiotic strains, LGG and S. boulardii, with sufficient evidence of efficacy in reducing the risk of antibiotic-associated diarrhea in children, based on data from well-designed randomized trials (1).

However, this study has several limitations. Firstly, the number of cases analysed was limited, with more robust outcomes needed for conclusive results. Secondly, the lack of fecal microbiome analysis is a significant gap, as the variability of gut microbiota among individuals may impact the response to probiotics. However, the study's strength is that it chose a probiotic supplement that contains strains that other research has shown to have a beneficial impact on general health (49,50).

CONCLUSIONS

The findings of this preliminary study indicate that administering a specific combination of probiotics as a preventive measure could benefit pediatric patients by enhancing their overall health and immunity. This intervention not only improves serum biochemical parameters but also enhances nutritional absorption capacity. The study suggests that for optimal results, probiotics should be taken for a minimum of five weeks. However, additional research is needed to refine recommendations for patient prevention and treatment strategies.

Author Contributions

Conceptualization, F.I., L.C., I.R.B., G.D., P.N. A.P., M.G. and A.D.I.; methodology, F.I., G.D., A.P., L.C., L.B, A.M. and A.M.I.; software, A.D.I., A.P., and G.D.; F.C.T.; validation, A.M.I., F.I., G.D., A.D.I., and F.I.; formal analysis, A.D.I., F.I., A.M., P.M., P.N., A.M.I., A.P., and G.D.; resources, A.D.I., A.M.I., A.P., F.I, L.C., and G.D.; data curation, A.M.I., F.I., A.M.I., A.D.I., L.C.; P.N., and G.D.; writing—original draft preparation, F.I., A.D.I., A.M.I., M.P., L.C., P.N.; F.C.T., and G.D.; writing—review and editing, A.P., A.M., I.P., M.G., L.C., P.N., F.I., G.D., A.M.I., and A.D.I.; visualization, A.M.I., F.I., A.D.I., P.M., D.C., G.D., and A.P.; supervision, G.D., F.T. L.C., P.N., A.D.I., A.M.I., A.P., and F.I.; project administration, G.D., A.M.I., A.D.I., and F.I. All authors have read and agreed to the published version of the manuscript.

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Consent Statement

Not applicable.

Data Availability Statement
Data are contained within the article.

Conflict of interest
The authors declare that they have no conflict of interest.

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