Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i6.6878

IMPACT OF PROBIOTIC CONSUMPTION ON GASTROINTESTINAL HEALTH: A REVIEW OF RANDOMIZED TRIALS

Dr Muhammad Asjad Abbas[1], Dr Hashim Mahmood[2], Dr Arshiya Sehar Hashmath[3], Dr Maha Hasan[4], Dr Rana Anees Ur Rehman[5], Dr Mais Abd Aziz Mohammad[6], Dr Rania Mahmoud Taha[7], Dr Ayesha Anwar[8], Dr Muhammad Ali Hassan[9*]

[1]Shifa College of Medicine/Shifa International Hospital Islamabad Pakistan.
Email: m.asjadaa@gmail.com, Orcid ID: https://orcid.org/0009-0007-7415-2989
[2]University College of Medicine and Dentistry Lahore, Pakistan
Email: hashim252000@gmail.com, Orcid ID: https://orcid.org/0009-0002-7982-627X
[3]Dr.NTR University of Health Sciences, Email: arshiyahashmath07@gmail.com
[4]Medcare Hospital UAE. Email: maha.hasan.ns35@gmail.com, Orcid ID: https://orcid.org/0009-0003-9105-8610
[5]Shifa International Hospital Islamabad, Email: draneesurrehman1@gmail.com
[6]Medcare Hospital UAE. Email: maismoh99@gmail.com , Orcid ID: https://orcid.org/0009-0000-2980-1280
[7]College of Medicine, University of Sharjah, Sharjah, United Arab Emirates, Email: u18100236@sharjah.ac.ae, https://orcid.org/0009-0009-6056-5023
[8]Chengdu Fifth People's Hospital, China, Email: ayeshaeta@gmail.com, Orcid ID: https://orcid.org/0009-0001-6938-2145
[9*]Shifa College of Medicine/ Shifa International Hospital Islamabad Pakistan, Email: alihassan0260060@gmail.com

***Corresponding Author:** Dr Muhammad Ali Hassan
*Email: alihassan0260060@gmail.com

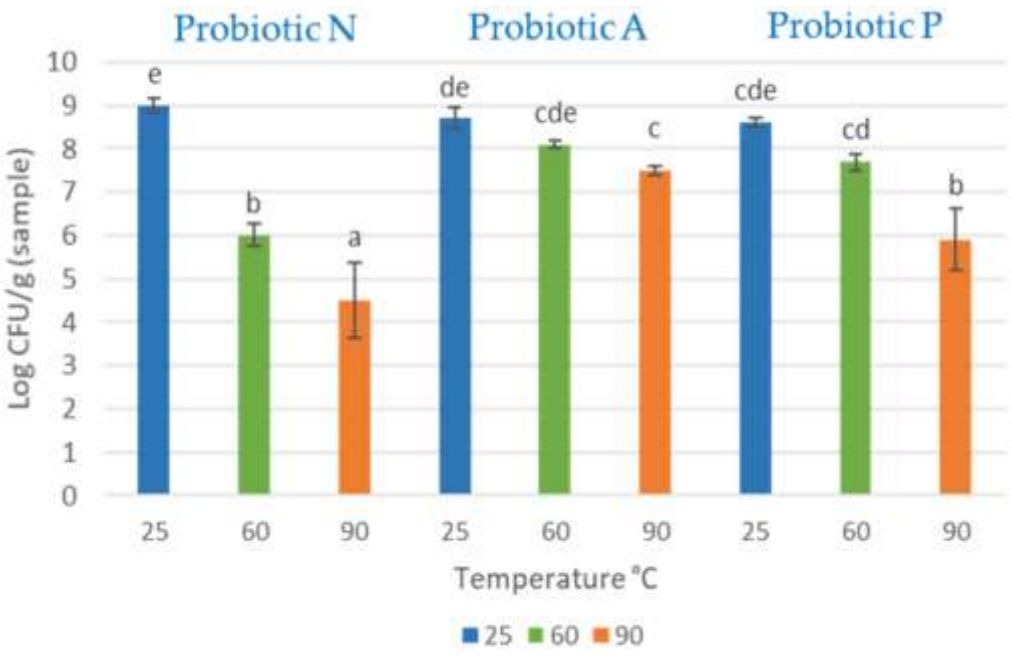
ABSTRACT
Multiple lines of evidence now support the notion that gut microbiota can contribute to digestive and extra-digestive diseases. The emergence of these observations enabled to postulate a bacteria-centric paradigm to rethink the treatment of many diseases. The goal of therapy should not be to eradicate the flora but to modify it in a way that leads to symptomatic improvement; thus, the interest in the use of probiotics to modulate microbiota composition has increased worldwide in both community and healthcare settings. Summary: The results of published studies are conflicting for most probiotic strains and formulations, and clinicians and consumers need a better understanding of probiotic risks and benefits. Currently, clear guidelines on when to use probiotics and the most effective probiotic for different gastrointestinal conditions are still lacking. Here, we reviewed the studies on the use of probiotics in some diseases of relevant interest to gastroenterologists, such as Helicobacter pylori infection, irritable bowel syndrome, and inflammatory bowel disease.

INTRODUCTION
Growing awareness of the importance of gut health and the gut microbiome is driving an increase in interest in probiotics and prebiotics that have the potential to improve not only gut health but also overall health, including immune health. The effects of probiotic supplementation on fecal microbiota

composition in healthy adults have not been well established. We aimed to provide a systematic review of the potential evidence for an effect of probiotic supplementation on the composition of human fecal microbiota as assessed by high-throughput molecular approaches in randomized controlled trials (RCTs) of healthy adults. The therapeutic effect of probiotic supplementation has been studied in a broad range of diseases, particularly in regard to gastrointestinal and metabolic disorders where results have supported the potential use of probiotics as therapeutic agents. Common to both sets of disorders is a multitude of readily available, clinically relevant outcome measures (e.g. body mass index, fat mass, insulin resistance, severity of gastrointestinal symptoms) by which to measure treatment effect. The effect of probiotics in disease-free individuals is, however, not as easily assessed. Interpretation of an effect on the composition of fecal microbiota in healthy individuals may be particularly complicated due to the lack of an internationally accepted consensus definition of a normal or a healthy fecal microbial community.

Characteristics of Probiotics:

Probiotics are live microorganisms, mostly bacteria and also a few yeasts. They are identified by their specific strain, which includes the genus, the species, the subspecies (if applicable), and an alphanumeric strain designation. The seven most common geniuses, or genera, used in probiotic products are Bifidobacterium, Lactobacillus, Saccharomyces, Streptococcus, Enterococcus, Escherichia and Bacillus. Strain designations are important in the clinical setting because they link clinical benefits (e.g. prevention of certain specific types of diarrheas) with both specific strains, and mixtures of specific strains, in effective doses. Some strains have unique properties (e.g. neurological, immunological or endocrinological effects) that may be linked to their specific clinical benefits.

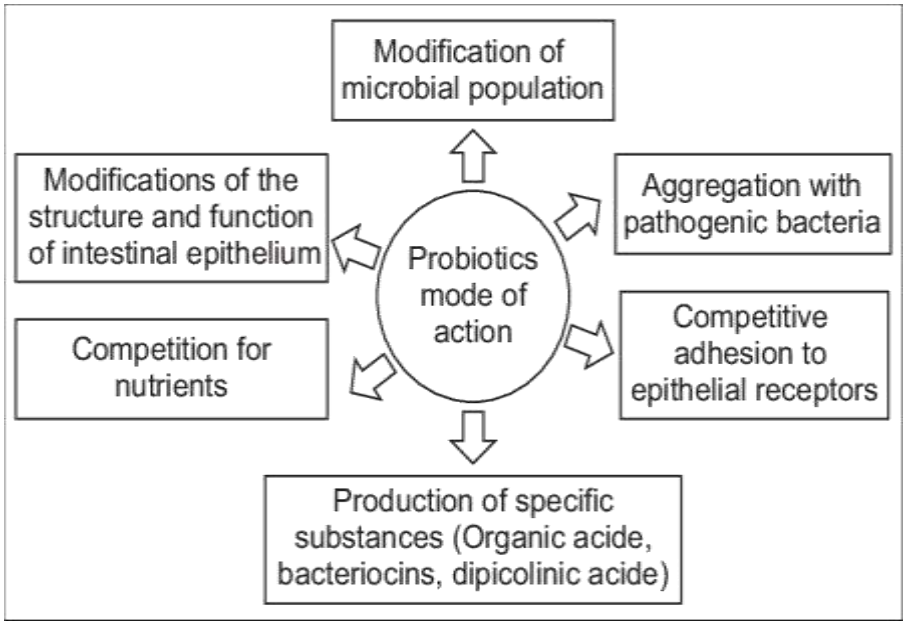


However, evidence is emerging that some mechanisms of probiotic activity are shared among different strains, species and genera. For example, the production of Short Chain Fatty Acids (SCFAs) in the colon, such as lactate and acetate and the ability to reduce gastrointestinal pH, is shared by most species of Bifidobacterium and Lactobacillus and many of their strains. These SCFAs contribute to general gut health and provide a range of potential health benefits both in and beyond the gastrointestinal tract (e.g. in terms of the immune system, brain, metabolic function). In a 2017 practice guideline, the World Gastroenterology Organization suggested that if the aim is to support digestive health, it is possible that many different probiotic preparations containing adequate amounts of single, or mixtures of well-studied, live microorganisms will be sufficient to provide a health benefit.

Probiotic products are available mainly in the form of dietary supplements, including tablets, capsules, powders, liquids and other formulations. Probiotics are also added to commercial yogurts and cultured milk drinks.

Fermented Foods and Drinks:

Traditionally fermented foods such as kefir, kombucha, sauerkraut and sourdough may contain live microorganisms but the microbes may not be fully characterized in terms of the bacterial strains present, the amounts of microbes present, whether the amounts present would confer a health benefit and whether the microbes are alive at the time of consumption. The opinion of the International Scientific Association for Probiotics and Prebiotics (ISAPP) is that these foods and drinks do not meet the definition for a probiotic product since they are largely uncharacterized and their health benefits unconfirmed. The ISAPP takes the view that if a probiotic microorganism or mixture of organisms is added to a fermented food or drink then that food or drink is a probiotic product.

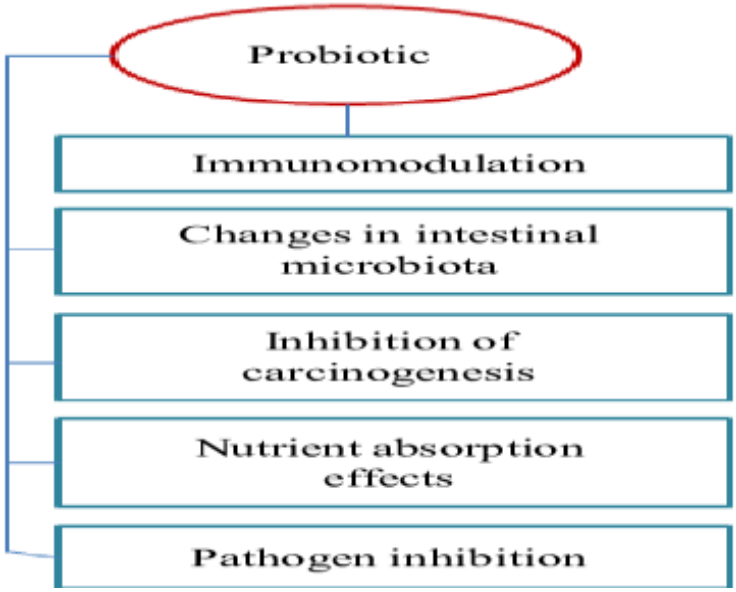


Nevertheless, consumption of traditionally fermented foods and drinks has been associated with health benefits. Fermented dairy products (mainly yogurt) have been associated in epidemiological

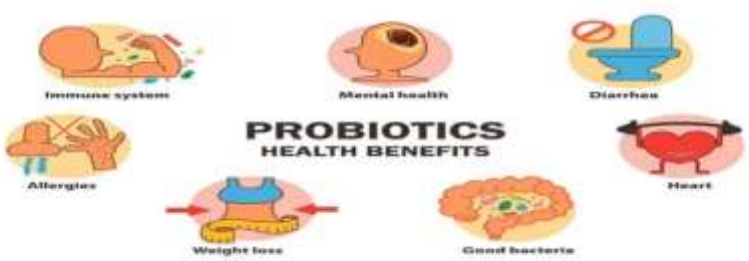
studies with reduced risk of metabolic syndrome, reduced risk of obesity, reduced risk of cardiovascular disease and reduced risk of colon cancer. Consumption of fermented soy products, such as miso and natto, has been associated with reduced risk of high blood pressure and reduced risk cardiovascular disease. Conversely, in the Netherlands cohort (34,409 Dutch men and women aged 20-70 years) of the large European Prospective Investigation into Cancer and Nutrition (EPIC) study, consumption of fermented dairy foods was not associated with mortality, cancer or cardiovascular disease.

Mechanisms of Action of Probiotics and Prebiotics:

The mechanisms of action of both probiotics and prebiotics relate to their influence on the microbes that inhabit the gastrointestinal (GI) tract. Approximately 100 trillion microorganisms (bacteria, viruses, fungi, protozoa) of at least 1000 different species live in the GI tract. Relatively few – mainly Lactobacilli and Streptococci – are found in the stomach and duodenum where gastric acid, bile and pancreatic juices inhibit or eradicate most microorganisms.



Lower down in the intestine, numbers of microbes progressively increase, from 104 cells per gram in the jejunum to 109 cells per gram of contents in the distal ileum. The colon is the most heavily populated region of the GI tract – mainly with anaerobic microbes - containing to 1012 cells per gram of intestinal contents. The diversity of gastrointestinal microbes between individuals is striking, with each individual harboring his or her own distinctive pattern of microbial composition. This is determined by genotype, initial colonization at birth and by dietary habits. In healthy adults, the faucal composition is stable over time. In the human gut, two bacterial divisions predominate Bacteroidetes and Firmicutes-and account for more than 90% of microbes. However, populations of colonizing microbes differ between healthy individuals and others with disease or poor health. Microbial composition also appears to differ according to age, sex, race and different geographical locations. However, researchers are still not entirely able to define the composition of a healthy human microbiota.



The ‘gut microbiota’ is the combination of microorganisms present in the GI tract. The ‘gut microbiome’ includes these microorganisms and also the genes associated with them and the environment that influences them. The gut microbiome, which is unique to each individual, contains over 3 million genes making it 130 times more genetically varied than the human genome which consists of about 23,000 genes. The gut microbiome can be considered as an organ in its own right. It produces thousands of active metabolites, which can affect human health and disease both inside and outside of the gut.

Gastrointestinal Conditions:

Probiotic supplementation has also been shown to be effective in preventing Antibiotic Associated Diarrhea (AAD) and/or Clostridium difficile diarrhea with higher doses being the most effective in these conditions. Both Lactobacillus rhamnoses GG and Saccharomyces boulardii have been shown to reduce the risk of AAD in the studies in these metaanalyses. Six recent meta-analyses have shown that probiotics induce remission in Inflammatory Bowel Disease (IBD), with most evidence of effectiveness for Ulcerative Colitis (UC), but less so for Crohn’s Disease (CD). Specific strains are likely to be important in IBD and further research is required to evaluate the place of probiotics in management of IBD and their use alongside usual care. There is also good evidence for the use of certain strains of probiotics for preventing an attack of paucities and in preventing further attacks after induction of remission. The effectiveness of probiotics for maintenance of remission in IBD is unclear. Studies have used various probiotic strains and combinations including Lactobacillus rhamnoses GG and Saccharomyces boulardii, various others strain of lactobacilli, bifidobacteria and Streptococcus thermophilus. Evidence from a further six meta-analyses also show a modest benefit with probiotics in the management of symptoms of irritable bowel syndrome (IBS), including constipation dominant IBS in which probiotics a

Health Outcome	Number of Studies	Findings
Travellers Diarrhoea (TD)	11 RCTs n=1227 (probiotics)	Significant efficacy in prevention of TD
Incidence of Traveller’s Diarrhoea (TD)	12 RCTs in systematic review; 6 RCTs in meta-analysis (probiotics)	One of three probiotics (Saccharomyces boulardii) showed significant efficacy for the prevention of TD. L. rhamnosus GG showed a trend and L. acidophilus no significant effect.
Treatment of acute diarrhoea in children	12 studies n = 744 children (probiotics)	Probiotics shortened duration of diarrhoea, improved 2-day treatment efficacy and reduced hospital stay
Acute infectious diarrhoea	82 studies/ n = 12127; 11526 children;412 adults (probiotics)	Probiotics probably make little or no difference to the number of people who have diarrhoea lasting 48 hours or longer. Whether probiotics reduce duration of diarrhoea is uncertain
Prevention of	33 studies n = 6352 children	Moderate protective effect of probiotics for preventing AAD

antibiotic associated diarrhoea (AAD)		
Prevention of AAD	42 studies n = 11305 (probiotics)	Probiotics are effective for preventing AAD. Secondary analyses of higher dosages and certain species have shown increased effectiveness.

associated with an increased bowel frequency and stool consistency. Most studies have employed strains of Lactobacilli and Bifidobacteria. In a metanalysis of 15 RCTs, consumption of probiotics, in particular, multispecies probiotics, substantially reduced the gastrointestinal transit, increased the stool frequency, and improved the stool consistency. Evidence for impact of prebiotics in IBS is scarce.

CONCLUSION:

Probiotics have a well-established evidence base in the prevention and management of gastrointestinal diseases such as traveler's diarrhea, antibiotic associated diarrhea and Clostridium difficile diarrhea. Other bowel conditions where they have a demonstrable clinical impact include ulcerative colitis, specifically in remission rather than maintenance, with less evidence of benefit in Crohn's disease. They have also been shown to tackle some symptoms of irritable bowel syndrome, lactose intolerance and constipation. Systematic reviews have also demonstrated the benefit of probiotics in preventing eczema in children, whether taken by the pregnant and/or breast-feeding mother or the infant. Although the health effects of prebiotics are emerging, they have been shown to be beneficial for the health of the gastrointestinal tract, inhibiting pathogens and stimulating immune function. Emerging evidence indicates that probiotics positively impact brain health with data from RCTs and systematic reviews indicating benefits in dementia, depression, Parkinson's disease, in cardiometabolic health and obesity, and in respiratory health, reducing the risk of upper respiratory tract infection, asthma, bronchitis and chronic obstructive airways disease. People with gut dysbiosis who have contracted COVID-19 seem to be at higher risk of more severe disease and death, suggesting that probiotics could be considered for the purpose of maintaining a healthy gut microbiota. These effects on organs distant from the gut arise as a result of communication between the gut microbiota and these organs through immune cells, inflammatory mediators, neurotransmitters and hormones. These findings, whilst requiring much more research in terms of health outcomes, represent exciting possibilities for the future of probiotics and prebiotics.

REFERENCES

1. De Vos WM, Tilg H, Van Hul M, Cani PD (2022) Gut microbiome and health: mechanistic insights. Gut 71: 1020-1032.
2. Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, et al. (2013) Health benefits of probiotics: a review. ISRN Nutr 2013: 481651.
3. Ezepchuk YV, Kolybo DV (2016) Nobel laureate Ilya I. Metchnikoff (1845-1916). Life story and scientific heritage. Ukrainian Biochemical Journal 88: 98-109.
4. Goodman C, Keating G, Georgousopoulou E, Hespe C, Levett K (2021) Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis. BMJ Open 11: e043054.
5. Nozue M, Shimazu T, Charvat H, Mori N, Mutoh M, et al. (2021) Fermented soy products intake and risk of cardiovascular disease and total cancer incidence: The Japan Public Health Center-based Prospective study. Eur J Clin Nutr 75: 954-968
6. Vijay A, Astbury S, Le Roy C, Spector TD, Valdes AM (2021) The prebiotic effects of omega-3 fatty acid supplementation: A six-week randomised intervention trial. Gut Microbes 13: 1-11.
7. Moreno-Indias I, Sánchez-Alcoholado L, Pérez-Martínez P, Andrés Lacueva C, Cardona F, et al. (2016) Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. Food Funct 7: 1775-1787.

8. Kristensen NB, Bryrup T, Allin KH, Nielsen T, Hansen TH, et al. (2016) Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. Genome Med 8: 52.
9. Mohr AE, Basile AJ, Crawford MS, Sweazea KL, Carpenter KC (2020) Probiotic supplementation has a limited effect on circulating immune and inflammatory markers in healthy adults: a systematic review of randomized controlled trials. J Acad Nutr Diet 120: 548-564.
10. Huang R, Xing HY, Liu H J, Chen ZF, Tang BB (2021) Efficacy of probiotics in the treatment of acute diarrhea in children: a systematic review and meta-analysis of clinical trials. Transl Pediatr 10: 3248- 3260.
11. Ma Y, Yang JY, Peng X, Xiao KY, Xu Q, et al. (2020) Which probiotic has the best effect on preventing Clostridium difficile-associated diarrhea? A systematic review and network meta-analysis. J Dig Dis 21: 69-80.
12. Chen M, Feng Y, Liu W (2021) Efficacy and safety of probiotics in the induction and maintenance of inflammatory bowel disease remission: a systematic review and meta-analysis. Ann Palliat Med 10: 11821- 11829.
13. Chen M, Feng Y, Liu W (2021) Efficacy and safety of probiotics in the induction and maintenance of inflammatory bowel disease remission: a systematic review and meta-analysis. Ann Palliat Med 10: 11821- 11829.