IJBPAS, November, 2025, 14(11): 5798-5813

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE EFFICACY OF PROBIOTIC SUPPLEMENTS IN ADDRESSING MALNUTRITION: A SYSTEMATIC REVIEW

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Received 15th July 2024; Revised 20th Sept. 2024; Accepted 21st Oct. 2024; Available online 1st Nov. 2025

https://doi.org/10.31032/IJBPAS/2025/14.11.9488

ABSTRACT

Malnutrition manifests as undernutrition or overnutrition. Micronutrient deficiencies are public health concern worldwide. There is evidence that probiotics can enhance micronutrient status, which could assist in the prevention of non-communicable diseases associated with malnutrition. This review assesses the evidence of the impact of probiotic to improve the status of micronutrients. The intake of certain specific probiotics was correlated with a beneficial effect on the status of several micronutrients. Malnutrition continues to imperil the existence of millions of people worldwide, with children being the most severely affected. The main causes of childhood malnutrition are inadequate access to food and infectious diseases, but the microbiota of the gut may also contribute. The diet affects the gut microbiota of children, which can thus affect their nutritional status. Malnutrition can hinder growth and weaken immune defense, increasing susceptibility to infections. Diarrhea, a significant cause of malnutrition, is broadly perceived by pathogenic components of the gut microbiota. Diarrhea results in poor absorption of certain essential nutrients and decreased energy availability resulting in weight loss. The term global malnutrition is connected to the usage of probiotics as a preventive method to reduce vulnerability in children and frailty in the elder. The risk of malnutrition combined with the frailty syndrome, with a history of poor microbiota during childhood, can make it difficult for the patient to recover and can even lead to death. Conversely, the probiotics when administered can make the intervention timelier and avoid severe complications, even with a fatal outcome.

Keywords: Malnutrition, Probiotics, Micronutrients, Gut microbiota, Childhood Nutrition

1. INTRODUCTION

Traditional fermented foods are a reservoir of active microbes and they are considered an important source of lactic acid bacteria (LAB) in nature **[1]**. Fermented foods are gaining much attention for the microorganisms that they carry, along with their nutritional values. These microbes are capable of synthesizing organic acids, vitamins, and peptides during fermentation. Microbes associated with food share similar genotypic and phenotypic traits to those present in probiotic strains **[2]**. Similar to probiotics, food-borne microbes survive in the gastrointestinal (GI) tract and they exert a beneficial impact on the host. It is estimated that large amounts of live lactic acid bacteria (approximately 10^8–10^{11} CFU/d) are ingested through the intake of fermented foods. The intake of fermented foods has numerous health advantages. Recently, there is an increase in epidemiological and clinical reports that confirm the benefits of lactic acid bacteria, associated with improvement in health and a reduction in disease risk **[3]**.

The World Health Organization (WHO) and the United Nations General Assembly, in 2016, executed the “United Nations Decade of Action on Nutrition 2016-2025” (WHO 2020), in which, there are joint efforts against any form of malnutrition, including malnutrition from childhood to that of the elderly. In this review, it is explained why malnutrition in childhood, should be prevented at this stage, depending on the intestinal microbiota, and what is the importance of the intake of probiotics on time. The economic and social inequalities and the climatic changes that have caused disasters and migrations in many places on the planet contributed to the increase in malnutrition throughout the world. In malnourished patients, other diseases are susceptible, especially to contracting infections and developing other non-infectious pathologies, derived from malnutrition, for which the intestinal microbiota plays a very important role.

2. PROBIOTICS

According to the Food and Agricultural Organization of the United Nations (UN) and the World Health Organization (WHO), probiotics are defined as 'live microbes which, when consumed in sufficient amounts, provide a health benefit to the host.' Strains belonging to the genera *Bifidobacterium* and *Lactobacillus* are the most commonly used probiotic bacteria, and they are included in many functional foods and dietary supplements **[4–6]**. Probiotics must meet specific criteria to be considered effective. This includes tolerating gastrointestinal conditions such as gastric acid and bile, adhering to the gastrointestinal mucosa, and excluding pathogens **[7, 8]**. They should also have a beneficial impact on the host while being free of adverse side effects, toxicity, or pathogenicity. Probiotics must survive the gastrointestinal (GI) tract and be present in sufficient quantities of viable cells within products to provide health benefits. Moreover, they should be compatible with product matrices and capable of withstanding processing and storage conditions. Finally, accurate labeling of probiotics is essential for ensuring proper use **[9]**. The results of analyses from human studies and animal models have shown the potential clinical effectiveness of probiotics in addressing various diseases **[10]**. Probiotics have been reported to suppress diarrhea **[11]**, alleviate lactose intolerance **[12]**, reduce symptoms of irritable bowel syndrome **[13]**, and prevent inflammatory bowel diseases **[14]**.

2.1 Health-Promoting Bacteria

Microorganisms play a significant role in the food processing industry. Among these, lactic acid bacteria, particularly of the genus *Lactobacillus*, are essential for dairy product manufacturing due to their acid-producing abilities. This group is divided into three main categories: obligate homo fermentative, facultative homo fermentative, and obligate heterofermentative **[15]**. The *Lactobacillus* genus comprises a diverse group of Gram-positive, rod-shaped, non-spore-forming, non-pigmented, catalase-negative bacteria that range from microaerophilic to strictly anaerobic bacteria **[16]**. Lactic acid bacteria have widespread applications in fermented food production and are also utilized in medical and veterinary fields **[17]**. "Lactobacilli isolated from dairy products have a long history of safe use in the food industry as starter cultures for products such as fermented milk, meat, sourdough, alcoholic beverages, and silage **[18]**. They naturally occur in raw milk and dairy products like cheese, yogurt, and fermented milk, contributing health benefits to consumers **[19]**. Lactic acid bacteria consist of various genera such as *Leuconostoc*, *Lactobacillus*, *Lactococcus*, *Enterococcus*, *Bifidobacterium*, *Pediococcus*, and *Streptococcus* **[20]**. Lactic acid bacteria are widely distributed in the environment and can inhibit the growth of pathogenic microorganisms **[21]**.

Scientific reports suggest that they may have anti-allergic and anticancer effects, promote fat loss, and enhance the host's immune response. They may also alleviate symptoms of irritable bowel syndrome, intestinal inflammation, and antibiotic-induced diarrhea **[22]**. *Lactobacilli* are Gram-positive and catalase-negative bacteria that constitute beneficial gut microflora and represent some of the most important probiotics **[23]**. Probiotics can stimulate the immune system and assist in the control of various diseases **[24]**. They are part of the natural flora of the mouth, intestine, and female genital tract and help regulate undesirable microorganisms. *Lactobacilli* aid in controlling unwanted gut microflora and inhibit the proliferation of pathogenic bacteria by producing antimicrobial metabolites. They can also serve as preservatives in foods **[25]**. "Three key factors for screening probiotics include antimicrobial activity, tolerance to bile salts, and acid tolerance **[26, 27]**. Lactic acid bacteria are resistant to gastric acid, gastrointestinal juice, lysozyme, and bile salts. They produce antimicrobial compounds that can inhibit pathogenic microorganisms and affect their metabolism **[28]**. Lactic acid bacteria provide protective effects in dairy products against harmful or pathogenic bacteria, and many studies have explored their antibacterial effects against Gram-negative and Gram-positive bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* **[29]**.

2.2 Safety properties

Many *lactobacilli* species have been classified as "Generally Recognized as Safe" (GRAS) by the Food and Drug Administration (FDA) and have received "Qualified Presumption of Safety" (QPS) status from the European Food Safety Authority (EFSA). Every strain used for industrial applications or as a probiotic must be thoroughly evaluated for safety using robust methods before it can be considered for use in real-life applications **[30]**. In 2019, EFSA published a public consultation outlining the criteria for whole genome sequence analyses of microorganisms that are part of the food chain, offering guidance for ensuring their safety and reliability.

2.3 Strain characterization for Probiotic attributes

Bacteria face several challenges when consumed by a person. They must survive through different conditions when exposed to low acid levels, bile, and other harsh environments. They also need to be able to stick to the cells that line the intestine. Starting in the mouth, an enzyme called lysozyme found in saliva can kill some bacteria. In the stomach, the low pH and the presence of other enzymes like lipase and pepsin can also harm bacteria. Once the bacteria reach the upper intestine, they encounter bile produced by the liver, which can be detrimental to them **[31]**. Therefore, an essential step in selecting potential probiotic candidates is to examine their tolerance to acid and bile. The lumen of the gastrointestinal (GI) tract contains commensal microbiota, a mucus layer, and epithelial cells. The monolayer of epithelial cells separates the intestinal mucosa, which is produced by goblet cells, and the commensal microbiota from immune cells, forming the gut epithelial barrier **[32]**. This intestinal epithelial barrier defends against infections and alterations to it have been associated with various diseases. Probiotics are a type of transient microbiome that, when consumed regularly, pass through the GI tract. While they may not be stable colonizers, their transient passage allows them to interact with commensal bacteria and epithelial cells, ultimately providing health benefits **[33]**.

3. MALNUTRITION

Malnutrition is a condition in which a person has either insufficient or excessive intake of certain nutrients. There are two primary forms of malnutrition: undernutrition and overnutrition. Undernutrition occurs when a person does not consume enough food or lacks the proper balance of nutrients, resulting in being underweight, wasting, stunting, or experiencing deficiencies in essential vitamins and minerals. On the other hand, overnutrition involves an excess of food intake, which can lead to obesity. In children, malnutrition can manifest in different ways. One way is underweight, where a child is thinner than their peers of the same age. Another is stunting, where a child is shorter than their peers of the same age, reflecting a lack of adequate growth. Wasting is another form, occurring when a child is too thin for their height, which can indicate recent or recurring infections or diarrhea **[34]**.

There are several causes of malnutrition, but they can be categorized into three groups according to UNICEF's 1990 framework: immediate, underlying, and basic causes. Immediate causes include inadequate dietary intake and illnesses such as diarrhea. The root causes are related to factors like household food insecurity, poor child care practices, limited health access, and inadequate sanitation, which contribute to poor dietary intake and illness among children. Basic causes encompass broader issues such as resource availability and the area's political, cultural, and economic conditions **[35]**.

3.1 Malnutrition in childhood

Excessive nutrient consumption can lead to obesity, representing the other extreme of malnutrition and generating disease **[36]**. According to the United Nations Children's Fund (UNICEF), the World Health Organization (WHO), and the World Bank (WB), 55 million children under the age of 5 were stunted in 2016, while 52 million were wasted, including 17 million who were severely wasted. In 2020, a slight decrease in these figures was reported, but there was an increase in the prevalence of obesity. Malnutrition in both children and the elderly is significantly related to low socioeconomic status **[37]**. Protein-caloric malnutrition, known as marasmus, is characterized by the loss of muscle mass and adipose tissue, resulting in patients with large-appearing eyes due to muscle thinness and adipose tissue. In contrast, kwashiorkor includes protein loss, hypoalbuminemia, and hemodilution, causing edema. Children under 5 years of age suffer from the most severe forms of malnutrition, which include long-term poverty-related malnutrition, poor hygiene and sanitation, inadequate nutrient intake, and exposure to infections and environmental aggressions. Environmental malnutrition in children leads them to a state of vulnerability, which can even lead to death **[38]**. From birth of human body, bacterial colonization of the gut strengthens the immune response and supports the maturation of organs and systems. The role of the microbiota, constitutes an important defense for the host since childhood **[39]**.

The establishment of the gut microbiota is typically completed by age of 3 years, unless other factors disrupt its composition **[40]**. This relationship between microorganisms and gut microbiota is relevant for the maturation of many functions of their organs and systems **[41]**. Malnutrition from childhood can delay linear growth and increase susceptibility to diarrhea. Early prevention can help to avoid linear growth retardation and related issues, such as weakened immune defense against pathogens causing diarrhea **[42]**. A study by Sanchez *et al*. found that Campylobacter negatively affects growth in children aged 12 to 21 months **[43]**. UNICEF and WHO reported a decrease in the prevalence of stunting from 39.7% in 1990 to 22.2% in 2017. Climate change is influencing the distribution and abundance of viruses, leading to the emergence of new strains or re-emergence of previously controlled viruses and pandemics. Examples of such viruses are HIV, Zika, and Ebola have caused significant illness and death in human populations.

3.2 Malnutrition in adults

Malnutrition is widespread across the globe, including among elderly individuals, who currently make up 8.5% of the world's population and are expected to nearly double by 2050. Frailty syndrome is defined by a decline in the function of multiple organs and systems, diminishing the ability to respond to internal and external stressors. Frailty is a state of vulnerability caused by various diseases, malnutrition, and other age-related conditions. Both malnutrition and frailty can lead to a significant decline in vital functions and increased susceptibility to infections, often with fatal outcomes **[44]**. Malnutrition affects 15% of elderly outpatients, 35% to 65% of hospitalized elderly patients, and 24% to 74% of institutionalized elderly individuals **[45]**. The prevalence of malnutrition varies across different countries and is linked to various factors, contributing to the loss of organ and system function and increasing the risk of death during infections **[46]**. The global rise in malnutrition and demographic shifts suggest that by 2050, the population of adults over 60 will increase from 900 million to 2 billion, representing 22% of the world's total population.

Neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) have a preclinical condition related to the composition of the intestinal microbiota **[47, 48]**. Emerging research suggests that certain intestinal bacteria and pathogens can disrupt normal physiological and metabolic pathways, affecting protein formation and leading to the defective accumulation of amyloid protein in specific areas of the brain. This contributes to the development of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS). In AD and PD, cognitive, sensory and non-sensory disabilities such as gastro paresis also occur **[49]**. There are five characteristic elements of frailty in the elderly: slowness, weakness, fatigue, low activity, and weight loss, fragility in mechanical performance due to malnutrition, vulnerability in energy metabolism, leading to inflammation and immune deterioration. They also cause a decline in bone quality, contributing to osteoporosis and an increased fear of repetitive falls and associated complications **[50-52]**.

4. ROLE OF PROBIOTICS

4.1 Modulation of Nutrient Status

Microorganisms have been suggested to play a role in modulating host micronutrient status due to their presence in food-associated transiting microbes. Probiotic and commensal bacteria in the human gut are known to synthesize vitamins **[53]**. Probiotics can enter the host through food or supplements. Despite of challenges such as gastric acidity and bile acids that can impede the viability of administered probiotics, they can survive in sufficient numbers to colonize and provide health benefits, including the production of vitamins **[54, 55]**. Probiotics could be a novel approach to improve the status of micronutrients and thereby combat non-communicable disease-associated malnutrition.

These benefits may occur through several mechanisms that optimize the intestinal microbiota for better nutrient absorption, including (a) decreasing pH via increased intraluminal lactic acid production **[56–58]**, (b) modifying hormone levels **[59]**, (c) beneficially altering gut microbiota populations **[60]**, and (d) inhibiting the adhesion of pathogenic bacteria to the intestinal epithelial cell surface, thereby reducing competition with the host for available nutrients **[61]**. Certain bacteria species, such as *Lactobacillus* and *Bifidobacterium,* can produce vitamins, particularly B vitamins and vitamin K. Improvement in the nutrient status following the administration of specific probiotics have been noted, especially in relation to B-group vitamins (folate and B12), as well as minerals (iron and calcium) **[62]**.

4.2 Gut Microbiota and Malnutrition

Inadequate food intake and diseases were recognized as the main immediate causes of malnutrition a few decades ago. However, enteric infections, such as diarrhea, have emerged as significant contributors to global malnutrition cases in children. These infections suggest a link between diarrhea and malnutrition through changes in the gut microbiota. Diarrhea can lead to malnutrition by decreasing nutrient absorption, causing mucosal damage, and resulting in nutrient loss **[63]**. Children who experience diarrhea may face reduced weight and height gains. According to the Global Enteric Multicenter Study (GEMS), moderate to severe diarrhea in children reduces bacterial diversity and alters microbiota composition **[64]**. Additionally, diarrhea in children under the age of two from low-income areas may lead to decreased height by the age of 7 to 9 years **[65]**. Early life diarrhea in children can impair gut microbiota development, resulting in persistent diarrhea, stunting, reduced IQ, and growth faltering. Prebiotic and probiotic interventions may support the microbiota in combating diarrhea and offer benefits in reducing malnutrition **[66]**.

4.3 Diarrhea and Malnutrition

Enteric infections such as diarrhea have been reported as a significant factor in a notable proportion of global malnutrition cases in children. Diarrhea can be categorized into two types:

A) Infectious Diarrhea

A Cochrane database review on the efficacy of probiotics for treating infectious diarrhea in both adults and children evaluated 63 studies with a total of 8,014 participants. The review found no adverse outcomes associated with probiotic interventions. Probiotics usage shortens the frequency of diarrhoea. Probiotics, when used alongside rehydration therapy, seem safe and offer clear benefits in reducing the frequency of diarrhea and lowering the frequency of stools in cases of acute infectious diarrhea **[67]**.

B) Antibiotic-Associated Diarrhea

A 2011 Cochrane review meta-analysis evaluated the results of 16 randomized parallel trials that investigated antibiotic-associated diarrhea in children between 0 and 18 years old who were receiving antibiotics **[68]**. The trials included treatment with various probiotic species such as *Bifidobacterium* spp., *Lactobacillus* spp., *Bacillus* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces spp*., and *Streptococcus* spp., either individually or in combination. The studies demonstrated a protective impact of probiotics, along with their dose and duration, in preventing antibiotic-associated diarrhea. Bernaola Aponte *et al*. **[69]** reviewed randomized parallel trials (RCTs) comparing specific probiotic agents with placebo or no probiotics in children with persistent diarrhea illness. The meta-analysis included a total of 464 participants from four trials. Probiotics treatment reduced the duration of persistent diarrhea in two trials. Additionally, two trials reported reduced stool frequency and one trial reported shorter hospital stay, although the participant numbers were very small. No adverse effects were reported. Alfaleh *et al*. performed a meta-analysis of 16 randomized parallel trials (RCTs) involving 2,842 infants of 37 weeks' gestation weighing 2,500 grams at birth. The trials considered various factors such as timing, dosing, probiotics formulations, and feeding regimens **[70]**.

4.4 Prevention of malnutrition using probiotics

Probiotics can help to establish a healthy intestinal microbiota, which can improve the composition of microorganisms and support of survival mechanisms in situations such as malnutrition. The world faces significant deficiencies leading to alarming rates of childhood malnutrition. Not everyone has access to proper nutrition and treatments necessary to recover their health and improve their functions. The intake of probiotics can help to restore the intestinal microbiota more promptly, preventing complications from malnutrition. Oral vaccination may not be as effective in inducing an immunogenic response as maintaining a healthy intestinal microbiota **[71]**. The intestinal microbiota administered through probiotics can positively modulate the organic functions of the host, influencing health and disease outcomes. Bacteria administered through probiotics can benefit the host, preventing health problems that may arise in old age, due to persistent alterations in the intestinal microbiota, installed in the host from childhood **[72]**. While probiotics are a well-studied and easily administered strategy for improving quality of life, they are not the only prevention tool. Other important prevention factors include exercise and healthy lifestyle choices in adulthood **[73]**. Nonetheless, probiotics remain a key component of an overall approach to preventing malnutrition and promoting well-being.

ACKNOWLEDGMENTS

The author would like to acknowledge the Department of Biotechnology & Microbiology of Atmiya University, Rajkot Gujarat for providing technical assistance.

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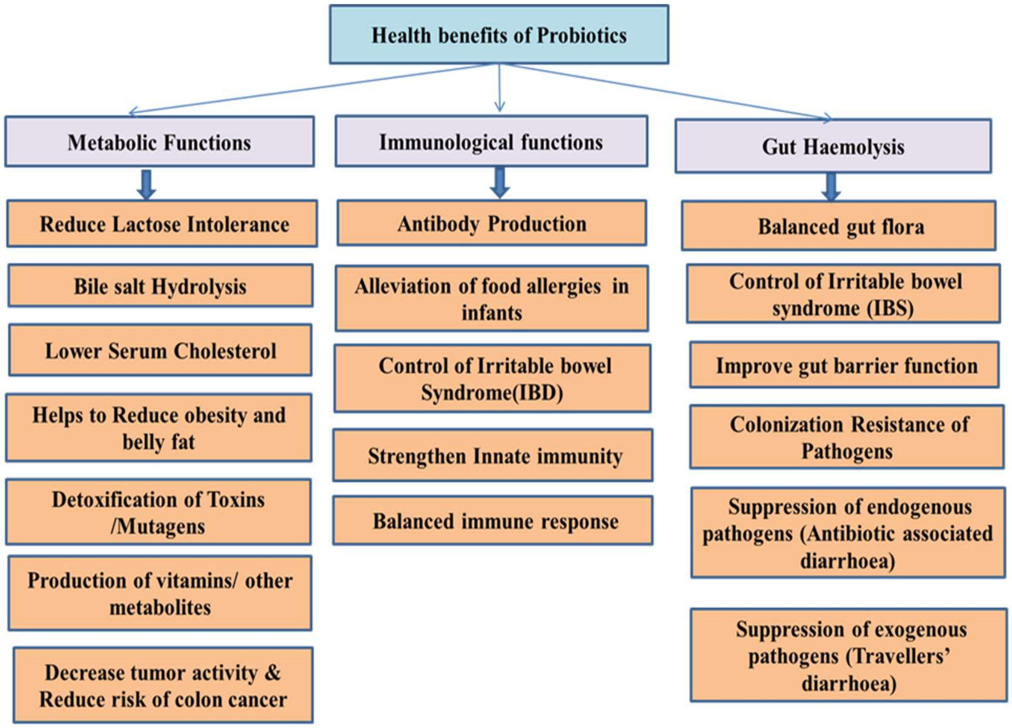

Figure 1: Health benefits of probiotics

Table 1: Effects of Poor Micronutrient Status during Childhood and Adolescence [74, 75]

Micro-Nutrient	Functions	Magnitude of the Problem	Health Consequences of Deficiency Disorders
Vitamin A	Essential for growth, immune function, and vision. Sources include liver, animal products, and certain fruits/vegetables.	5-7% of Indian children suffer from vitamin A deficiency-related eye disorders.	Night blindness, higher risk of infections, and increased risk of death from moderate deficiency.
Iron	Crucial for hemoglobin production and immune system function. Sources include cereals, beans, and spinach.	Affects over half the population, especially children and pregnant women.	Poor attentiveness, memory, and academic performance; low birth weights in infants.
Zinc	Necessary for immune system function, cell division, and growth. Sources include animal products and seafood.	Linked to reduced severity of diarrhea and respiratory infections.	Deficiency leads to impaired growth, development, and increased morbidity.
Iodine	Key for thyroid hormone production. Sources include dairy products, bread, and eggs.	Endemic in 235 Indian districts due to soil deficiency.	Causes goiter and preventable mental retardation.