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Review Article

Recent Advances in the Health Benefits and Safety of Probiotics: A Comprehensive Review

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Abstract:

Probiotics are live microorganisms that, when given in sufficient quantities, offer health benefits, and are essential for preserving the gut health and general well-being of humans. Probiotics have a wide range of beneficial impacts on human health, which include immunomodulation, improved gut barrier function, and competitive exclusion of pathogens. Research indicated that probiotics can help to lower the cholesterol levels and prevent and treat several illnesses, including cancer, lactose intolerance, irritable bowel syndrome, anemia, obesity, and allergy disorders. Probiotics also have a major impact on the composition of the gut microbiota, which helps to restore microbial balance and increase the number of beneficial bacteria. Probiotics due to their capacity to modulate the immune system and reduce inflammation have shown encouraging results when given as a supportive therapy to the patients during COVID-19. Probiotics are now easily available commercially worldwide as people are more frequently using for getting positive health benefits. Probiotics can be taken either in drink of dairy products or into foods or even can be consumed as supplements. Probiotic therapeutic applications will be further optimized as research progresses and the specific strains and formulations that maximize health benefits are understood. This review highlights the emerging role of probiotics in enhancing human health.

Key words: health benefits; health promotion; probiotics; therapeutic effects

1.Introduction

A large number of pathogens, mostly in the form of bacteria, are consumed by humans regularly. Because probiotics are good for human health, people have been adding them to different diets for several decades [1]. Probiotics have become widely used in functional meals in recent years; they can be found in food products and supplements alike. Probiotics are a crucial part of many dietary regimens because of their possible health benefits, which appeal to consumers [2]. Probiotics, sometimes referred to as "health-friendly bacteria," are live, non-pathogenic microorganisms that, when given in sufficient quantities, boost the host's health. Long-standing research has linked probiotics to improved human health, and as more and more clinical studies have shown these benefits, probiotics' appeal has grown [3].

The frequently used strains belong to the divergent group of *Bifidobacterium* and *Lactobacillus* that significantly affect health with various actions. They detoxify xenobiotics and environmental pollutants [4], bio-transform mycotoxins in foods [2]. synthesize vitamin K, riboflavin, and folate [2], and ferment undigested fiber in the colon [5]. Probiotics prevent pathogenic bacteria by restricting binding sites on mucosal epithelial cells and modulating the host immune response, thus improving intestinal barrier integrity [6]. The advantages of probiotics are related to the modulation of gut microbiota, mitigation of nutritional intolerances (lactose intolerance), increase in bioavailability of macro and micronutrients, and alleviation of allergic incidences in susceptible individuals [7].

Beneficial microorganisms, especially probiotics, play a crucial role in promoting human health through a symbiotic relationship with the body [8]. Probiotics, defined as microorganisms that provide health benefits when consumed in sufficient amounts, have attracted considerable attention for their ability to prevent and manage various diseases [9]. These probiotics offer a wide range of health benefits, including antimicrobial [10], anti-inflammatory [11], antioxidant [12]. and immunomodulatory effects [11]. They can also help people who can't handle lactose [13], fight diarrheal diseases [14], treat ulcers [15], boost immune systems [16], keep food fresh [17] and may be even lower the risk of colon cancer [18].

Probiotics actively influence and regulate the host's immune system by triggering the activation of specific genes in localized host cells. They also modulate the release of gastrointestinal hormones and affect brain behavior through bidirectional neuronal communication, forming part of the gut-brain axis [19]. Furthermore, probiotics play a crucial role in promoting intestinal angiogenesis via vascular endothelial growth factor receptor (VEGFR) signaling, which helps control acute and chronic inflammation in intestinal mucosal tissue, particularly in the context of inflammatory bowel disease (IBD) [20]. Additionally, probiotics contribute to maintaining a healthy microbial balance within the host and have been found effective in combating issues like overweight and obesity [21]. The present communication delineates the essential role played by probiotics due to their several health benefits for promoting human wellbeing.

2. General characteristics of probiotic

Probiotics are live microorganisms that, when consumed in sufficient quantities, offer health benefits to the host, particularly by supporting gut health and boosting immune function. A key attribute of probiotics is their resilience in the gastrointestinal environment, where they must withstand challenges such as stomach acid and bile salts to be effective [22]. Additionally, probiotics display strain-specific actions, meaning that different strains produce unique health effects, making it essential to select the appropriate strains based on targeted health objectives [23].

For probiotics to be functionally effective, they must adhere to mucosal surfaces, allowing them to colonize the gut and interact with host cells [24]. Additionally, probiotics affect the synthesis of immunoglobulins and cytokines, which help modulate immune responses, promote immune balance, and potentially reduce inflammation [25]. Moreover, many probiotics produce antimicrobial substances, such as hydrogen peroxide and lactic acid, inhibiting harmful bacteria's growth and enhancing overall gut health [26].

Probiotics are generally considered safe (GRAS) when taken in appropriate amounts, with few adverse effects seen in healthy individuals; however, caution is advised for immunocompromised populations [27]. When combined with prebiotics, probiotics can also demonstrate synergistic effects, further improving gut health and function [28]. Another key feature of probiotics is their ability to ferment dietary fibers, producing short-chain fatty acids (SCFAs) that have anti-inflammatory properties and supply energy to colon cells [29].

3. Mechanisms action of probiotics

Probiotics help the human body in a number of important ways, including immunomodulation, improved intestinal barrier function, competitive exclusion of pathogens, and neurotransmitter synthesis. Probiotics prevent dangerous microorganisms in the gut from surviving by competing with pathogens for resources and receptor-binding sites [30]. Furthermore, they function as antimicrobial agents by the production of compounds that decrease harmful microorganisms, including bacteriocins [31], hydrogen peroxide [32], organic acids, and short-chain fatty acids (SCFAs). By inducing the production of mucin proteins [33], controlling the expression of tight junction proteins like occluding and claudin-1, and modifying the immune response in the gut, probiotics also improve the function of the intestinal barrier [34].

Probiotics regulate both the innate and adaptive immune responses by modulating dendritic cells (DCs), macrophages, and B and T lymphocytes. They also enhance the production of anti-inflammatory cytokines, interacting with intestinal epithelial cells to recruit macrophages and mononuclear cells [35]. Additionally, probiotics contribute to neurotransmitter production in the gut through the gut-brain axis. Certain probiotic strains can modulate serotonin, gamma-aminobutyric acid (GABA), and dopamine levels, impacting mood, behavior, gut motility, and stress-related pathways [36].

4. Properties of probiotics

When ingested in sufficient quantities, probiotics live microorganisms offer health advantages; nevertheless, their efficacy depends on some critical characteristics. Resistant to bad conditions in the gastrointestinal tract, such as bile salts and stomach acid, probiotics are needed to reach the intestines undamaged, which are one of their most important qualities [37]. Moreover, for them to effectively colonize and carry out their health-promoting activities, they must be able to stick to intestinal epithelial cells [24]. Probiotics also have antibacterial qualities by generating substances like lactic acid, hydrogen peroxide, and bacteriocins, which inhibit pathogenic bacteria and promote gut health [26].

Probiotics also have an important effect on immunological regulation, which improves the host's immune response and lowers inflammation by increasing the synthesis of immunoglobulins and anti-inflammatory cytokines [25]. Additionally, probiotics have metabolic activity because they digest dietary fibers to create short-chain fatty acids (SCFAs), which have anti-inflammatory and energy-giving properties for colon cells [29]. Probiotics occupy gut niches through a process known as competitive exclusion, which means they compete with harmful bacteria for resources and lower the risk of infection [38].

Probiotics also improve intestinal barrier integrity, stop "leaky gut," and guard against pathogen and toxin translocation, all of which support the function of the gut barrier [39]. Probiotic strain specificity emphasizes that various strains can produce varying health advantages, highlighting the necessity for careful selection based on intended health outcomes [40]. According to Millerand co-others [27] probiotics are generally regarded as safe (GRAS) and rarely cause side effects in healthy people. However, persons with impaired immune systems should exercise caution when using them. Last but not least, probiotics and prebiotics can work in concert to improve gut health and functionality overall [28].

5. Therapeutic effects of probiotics

Probiotics offer numerous health benefits, potentially preventing and reducing various diseases, including allergic diseases, cancer, hypercholesterolemia, lactose intolerance, inflammatory bowel disease, diarrhea, and irritable bowel syndrome [9, 41]. Key benefits of probiotics include reduced vulnerability to infections, alleviation of lactose intolerance symptoms, relief from allergic episodes and respiratory infections, lowering serum cholesterol and blood pressure, protection against gastritis and diarrhea, prevention of urogenital and vaginal infections, and reduced risk of colon cancer [42]. Probiotics are manufactured by several pharmaceuticals and are readily available at the shops [9]. Currently, probiotics are prescribed by the physicians and dieticians to the patients for keeping good health [Pratibha Dave, Personal Observation].

5.1. Antiallergic effect of probiotics

Probiotics may enhance the gut's endogenous barrier mechanisms, alleviating intestinal inflammation and serving as a valuable tool in the treatment of food allergies [43]. Their beneficial effects on allergic reactions are thought to arise from improved mucosal barrier function and immune system stimulation, which may help control inflammation associated with hypersensitivity reactions in patients with atopic eczema and food allergies [44].

Notably, the administration of *Lactobacillus rhamnosus* GG has been linked to a decreased incidence of eczema in infants [45]. Probiotics, particularly strains of *Lactobacillus* and *Bifidobacterium*, show promise in mitigating the severity of allergic conditions such as eczema and allergic rhinitis. They may help regulate immune responses to allergens and support skin barrier function, thereby reducing inflammation [46].

5.2. Probiotics in Gastrointestinal Diseases

Probiotics have proven to be beneficial in managing several gastrointestinal disorders, including diarrhea, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and constipation. They are particularly effective in treating acute infectious diarrhea and antibiotic-associated diarrhea by restoring the balance of gut microbiota and producing antimicrobial substances [47, 48].

In the case of IBS, specific strains like *Bifidobacterium infantis* can alleviate symptoms by reducing inflammation and improving gut health [49]. Additionally, probiotics, such as *Escherichia coli* have shown positive effects in maintaining remission in ulcerative colitis [50]. Probiotics also offer benefits in relieving constipation and can serve as an adjunct therapy in eradicating Helicobacter pylori infections [51, 52].

5.3 Lactose Intolerance

The most extensively studied health benefit of probiotics is their ability to enhance lactose digestion and alleviate intolerance symptoms in individuals with lactose malabsorption, characterized by insufficient activity of the lactose-cleaving enzyme β-galactosidase in the small intestine. Fermented milk products containing probiotics survive the passage through the stomach and reach the small intestine, where they support lactose hydrolysis through their enzymes [53, 54].

Furthermore, probiotic bacteria contain high levels of lactase, which is released into the intestinal lumen when these bacteria are lysed by bile secretions. This lactase then acts on ingested lactose, helping to reduce symptoms of maldigestion [54].

5.4 Anti-pathogenic activity

Many probiotics are known to produce antipathogenic compounds, ranging from small molecules to bioactive antimicrobial peptides [55]. The lowering of pH through the production of acids like lactic and acetic acid exerts bactericidal and bacteriostatic effects [56]. Additionally, the production of hydrogen peroxide (H_2O_2) by probiotic strains can have antimicrobial effects by oxidizing sulfhydryl groups, leading to the denaturation of various enzymes as well as causing the peroxidation of membrane lipids, which increases membrane permeability [57].

Probiotics also produce antimicrobial peptides and bacteriocins. The antimicrobial action of these compounds involves increasing the permeability of the cytoplasmic membrane of target cells, resulting in the release of small cytoplasmic particles, membrane depolarization, and ultimately cell death [58].

In addition to generating antimicrobial compounds that act directly on pathogens, probiotics may stimulate host antimicrobial defense pathways. The intestinal tract has several mechanisms for resisting pathogens, including the production of defensins cationic antimicrobial peptides produced by various cell types, such as Paneth cells in the crypts of the small intestine and intestinal epithelial cells. Probiotics may enhance the synthesis of defensin expression or produce proteases that activate defensins in the intestinal lumen [55].

5.5 Prevention of inflammatory bowel disease

The gastrointestinal tract plays a crucial role in protecting the body from toxic and infectious substances. However, factors such as stress, unhealthy diets, dysbiosis, and antibiotic treatments can compromise intestinal microbiota and barrier function, leading to increased permeability. This disruption may contribute to diseases like inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), as well as extra-intestinal conditions, such as heart disease, obesity, and type 1 diabetes [59].

An unidentified cause and an intensified immune reaction to the body's gastrointestinal (GI) microbiota, which mainly affects the colon and duodenum, are the hallmarks of inflammatory bowel disease (IBD). Usually, it is divided into two primary categories: ulcerative colitis (UC) and Crohn's disease (CD). Although previous research focused on adaptive immune responses as the main cause of these disorders, more recent research has brought attention to the important function of the innate immune system [60].

The innate immune response can disrupt the balance between the gut's beneficial microbiome and commensal microflora, leading to dysbiosis. This imbalance can intensify inflammatory responses, thereby influencing the development of IBD [61]. Probiotic administration may alleviate IBD symptoms or help maintain remission by regulating the inflammatory response, enhancing barrier function to protect tight junctions, and modulating gut microbiota composition and activity [62].

5.6 Probiotics in cancer prevention and treatment

Probiotics have emerged as promising agents in the fight against cancer, demonstrating their potential in laboratory (in vitro) and animal studies (in vivo). Various probiotic strains have shown the ability to combat different types of cancer. For instance, *Lactobacillus* strains (such as *L. paracasei* SR4, *L. casei* SR1, and *L. casei* SR2) exhibit anticancer effects against cervical cancer cells (HeLa) by increasing the expression of apoptotic genes, including BAX, BAD, caspase-8, caspase-3, and caspase-9, while reducing the activity of the anti-apoptotic gene BCl-2 [63].

The cancer-preventive properties of probiotics are often attributed to bacteria found in fermented milk products. Several mechanisms have been proposed to explain these effects, which have been investigated in vitro and in animal experiments. These mechanisms include the inhibition of tumor growth and proliferation by glycopeptides and cytotoxic metabolites from lactobacilli, the reduction of (pro)carcinogenic, mutagenic, and genotoxic substances and cancer-promoting enzymes in the colon due to modifications in gut microbiota, and a decrease in pH along with chemical modifications [53].

5.7 Probiotics in the treatment of anemia

Numerous studies have highlighted a significant connection between gut microbiota and iron deficiency. Research has illuminated the reciprocal relationship between iron deficiency and the composition of gut microbiota, as well as the beneficial impact of probiotic bacteria on enhancing iron absorption [64].

Folic acid, a water-soluble B vitamin essential for addressing and managing anemia, can be derived from probiotic microbes, such as *L. lactis*, *L. cremoris*, *B. pseudocatenulatum*, *Candida famata*, *B. adolescentis*, *Candida glabrata*, *Candida guilliermondii*, *S. cerevisiae*, *Yarrowia lipolytica*, and *Pichia glucozyma*. These microbes enhance intestinal absorption of folic acid. Additionally, *P. denitrificans* and *P. shermanii* have proven useful in treating vitamin B12 deficiency. Lactic acid-fermented foods play a crucial role in increasing iron absorption and

are often utilized in managing anemic patients. These foods help optimize the pH of the digestive tract and activate the enzyme phytase, which is important for nutrient absorption. Moreover, a combination of probiotic bacteria has been incorporated into food products to treat megaloblastic anemia, promoting colonic fermentation and counteracting the adverse effects of antibiotics [65].

5.8 Probiotics in the treatment and prevention of obesity

Numerous medical disorders, such as type II diabetes, coronary heart disease, and hypertension, are significantly increased by obesity. Obesity is caused by a variety of factors, including dietary preferences, levels of physical activity, age, heredity, and developmental stage [66]. Recently, probiotic microorganisms have become involved in the development of a unique strategy for managing and decreasing obesity. By controlling food intake, encouraging longer feelings of satiety, decreasing fat deposition, improving energy metabolism, and raising insulin sensitivity, probiotics have shown their ability to successfully prevent weight gain and obesity [67].

Furthermore, microbiota transfer from a healthy individual to an obese person can alter the composition of the recipient's microbial flora. Recent studies have also shown that probiotics play a role in reducing serum cholesterol levels through mechanisms involving the production of short-chain fatty acids and the conjugation of bile salts [68, 69].

5.9 Probiotics in COVID-19

Probiotics have attracted attention as a supportive therapy in managing COVID-19 due to their capacity to modulate the immune system and reduce inflammation. They are thought to influence the gut-lung axis, which is vital for respiratory health, as it connects gut microbiota to immune responses in the lungs. Probiotic strains, particularly *Lactobacillus* and *Bifidobacterium*, may strengthen gut barrier function, decrease systemic inflammation, and boost antiviral defenses, potentially mitigating the severity of COVID-19 symptoms [70].

Probiotics may help the body produce more interferons and other antiviral cytokines, which help the body, fight viral infections, according to a number of studies [71]. Probiotics can aid in the restoration of dysbiosis caused by COVID-19, which further enhances immune system function in general and the gut microbiota in particular [72]. Patients with COVID-19 who use probiotic supplements report less severe symptoms, shorter hospital stays, and a decreased risk of developing secondary bacterial infections [73].

Although the initial results are encouraging, more clinical research is required to identify the best probiotic strains and dosages for the treatment of COVID-19. According to recent studies, probiotics can improve recovery and lessen consequences by modifying immunological and inflammatory pathways, even though they cannot prevent COVID-19 infection [74].

5.10 Other Health benefits of Probiotics

Through the regulation of anti-inflammatory cytokine production and the stimulation of the body's natural defenses, probiotics improve immunological function. According to Huang and co-investigators [75], they have the potential to mitigate the severity of common cold and influenza as well as aid in the prevention of respiratory infections. Gut health and mental health are related through the gut-brain axis. Through their effects on the gut microbiota, reduction of inflammation, and modulation of neurotransmitter synthesis, probiotics may help with the symptoms of anxiety, depression, and stress. Studies conducted by Liu and co-investigators [16] reported that probiotic supplements may enhance mood and cognitive performance. Additionally, probiotics may lower the risk of oral infections, such as dental caries and periodontal disease, by balancing oral microbiota. Certain strains, like *Lactobacillus rhamnosus*, have demonstrated potential in reducing harmful bacteria in the mouth [76].

Probiotics are vital for maintaining vaginal health because they help restore the proper balance of vaginal bacteria. They may help in the treatment and prevention of urogenital disorders, such as urinary tract infections (UTIs), bacterial vaginosis, and yeast infections [77]. Probiotics that specifically decrease cholesterol have also been linked to heart health benefits. They could lower LDL and total cholesterol by preventing the reabsorption of bile and dissolving it in the stomach [78]. Additionally, new studies indicate that probiotics may improve bone strength and density by decreasing inflammation and improving calcium absorption, which may reduce the risk of osteoporosis [79].

6. Conclusion and Recommendations

An increasing amount of research is pointing to probiotics' positive benefits on human health, including their potential to prevent and treat a wide range of illnesses. Their potential as therapeutic agents are enhanced by their modes of action, which include immunomodulation, intestinal barrier strengthening, and competitive exclusion of pathogens. Probiotics have a wide range of therapeutic applications, including the treatment of lactose intolerance, cholesterol control, cancer prevention, and allergy disorders. It is critical to keep researching the precise probiotic strains and formulations that optimize health benefits as research progresses. Probiotics' therapeutic applications can be further optimized by comprehending the influence of gut microbiota composition and individual variability in reaction to them. Through dietary interventions, probiotics constitute a promising path for boosting health and well-being, with the potential to improve quality of life.

The following recommendations are forwarded.

- ✓ Public health campaigns should promote the inclusion of probiotic-rich foods (like yogurt and fermented products) and supplements as part of a balanced diet to improve gut health and overall well-being.
- ✓ Since different probiotic strains have unique health benefits, healthcare providers should consider strain-specific probiotics tailored to individual health conditions, such as gastrointestinal disorders, allergies, or mental health issues.
- ✓ Medical professionals should consider incorporating probiotics as part of treatment regimens, especially for conditions such as IBD, antibiotic-associated diarrhea, and COVID-19 recovery, given their immune-boosting and gut health-enhancing properties.
- ✓ Emphasis is given to undertake further studies to elucidate the emerging role of probiotics in food industry.

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Contribution of authors

All authors contributed during the preparation of the manuscript.

Conflict of interest

There was no conflict of interest.

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