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Human Health and Probiotics: Present Understanding and Future Pathways

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Probiotics are live microorganisms that help the host's health when given in sufficient quantities. Because of its demonstrated and possible benefits for maintaining health and averting illness, they have become one of the most studied functional foods of the past 20 years. The word probiotic comes from the Greek meaning “for life,” highlighting their encouraging effect on human physiology. Probiotics are now commonly taken as functional drinks, nutritional supplements, or added to common meals like curd and fermenting milk products. According to the most recent scientific research, probiotics are crucial for immunity, metabolic control, mental health, and the treatment of chronic illnesses in addition to digestive health.

Keywords: Probiotics, therapeutic effect, gut, mood.

Introduction

Probiotics constitute live microorganisms (bacteria, yeast, etc.) and are beneficial for maintaining a healthy gut when consumed in appropriate amounts. Probiotics have been in use for ages, with evidence supporting their use by ancient Romans and Greeks in the form of fermented dairy produce since the onset of Middle Bronze Age (1). Advancements in the field of science have improved our knowledge with respect to the advantageous microorganisms, specifically the way these microbes influence gut health and quality of life. The World Health Organization (WHO) defines probiotics as “live microbes which confer a health benefit to their host when administered in adequate amounts” (2).

Humans are home to a great many microbes that comprise intricate ecosystems, referred to as microbiomes, in various tissues, including the alimentary canal, epidermis, oral-mucosa, and urothelium. The gut microbiota influences nutrient absorption, immune responses, cellular metabolism, and even nervous system functioning, which is why it is considered crucial in regulating human health (3).

Achieving “Gut homeostasis”, an equilibrium where the advantageous microbes supersede the potentially detrimental microbes to create an environment promoting sound health and disease control, is facilitated by Probiotics (4).

The growing attention for probiotics echoes a larger shift towards preventive medicine and naturalistic mediations. As researchers explore the intricate mechanisms substantiating gut health and overall well-being, probiotics have evolved from conventional leavening agents to advanced health supplements with implementation in various areas of medicine (5). This article assesses the recent take on the role of probiotics with respect to human health by investigating the intricate mechanisms and safety issues involved with their use, and potential applications.

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Probiotic: Sources, Forms, and Compositions

Commonly Found Probiotic Strains

Probiotic strains belonging to the *Lactobacillus* and *Bifidobacterium* genus have been in use for ages, and their safety and effectiveness has been substantiated scientifically. *Lactobacillus acidophilus, L. rhamnosus, L. casei, L. plantarum, Bifidobacterium longum,* and *B. breve* are a few of the most widely employed strains in probiotic formulations (6). Several microorganisms such as, *Bacillus, Streptococcus, Enterococcus,* and *Saccharomyces boulardii,* are also employed in probiotic formulations (7).

The inherent attributes and functionality of probiotic strains are unique, making the nutritional benefits of one strain completely different from the other strains, even when both strains belong to the same species (8). The specificity exhibited by probiotic strains is crucial in selecting the strains for specific health applications. Owing to the natural prevalence of *Lactobacillus acidophilus* in various human tissues, such as, oral mucosa, lungs, gastrointestinal tract, genitals, and urinary tract, these probiotic strains have wide applications (9).

Novel and Probiotic-Prebiotic Formulations (symbiotic)

Prebiotics are the non-digestible foods that specifically stimulate the proliferation of useful bacteria. Synbiotics, a combination of prebiotics and probiotics, improve the efficacy of probiotics to a greater extent. These combinations not only enhance the inherent viability and stability of probiotics but also inhibit the pathogens. Compounds such as oligosaccharides, fibers and various other substances found in certain foodstuffs (chicory roots, wheat, asparagus, onions, garlic, etc.) are considered prebiotics (10).

Advancements in the field of encapsulation have helped to overcome the hurdles related to designing probiotic formulations, improving shelf life, and absorption by the gastrointestinal tissues (11). Various encapsulation methods, ranging from spray drying, microencapsulation, and gel entrapment by employing different materials like CaCl2, natural biopolymers (Sodium alginate, polysaccharides), protect probiotics from unfavorable conditions (12). These methods improve the viability of probiotic formulations, enable sustained release, and minimize the losses during processing, thus encouraging the wider application of probiotics as nutraceuticals (13).

Table 1 illustrates the common microbes employed as probiotics

Table 1: Common probiotic strains and their applications

S. No	Strain	Category	Applications	References
1	*Lactobacillus acidophilus*	Bacteria	Gastrointestinal health, vulvo-vaginal microbiome, and immunological responses	8
2	*Bifidobacterium longum*	Bacteria	Anti-inflammatory activity, maintaining the intestinal-mucosa barrier	6
3	*Saccharomyces boulardii*	Yeast	Managing antimicrobial-induced diarrhea	7
4	*Lactobacillus rhamnosus GG*	Bacteria	Managing hospital-acquired diarrhea in kids	8
5	*Bifidobacterium infantis*	Bacteria	Management of Irritable bowel	6

Sources of Probiotics (Dietary and Supplementary

Fermented foodstuffs and dietary supplements are common sources of probiotics. Indigenous fermented food items such as kefir, kombucha, kimchi, and yogurt are a good source of active pools of beneficial bacteria. Though a good source, these indigenous foods lack enough concentration of probiotics in comparison to the supplements. However, these traditional foods provide greater nutritional coverage and biodiversity to the gut microbiome. Probiotics supplements are available in various forms, ranging from pills, capsules, powders, to suspensions, frequently providing highly concentrated forms of specific beneficial strains. Depending on one's health goals and therapeutic requirements, the source of the probiotics can be chosen (14).

Mechanisms Involved in Conferring Health Benefits:

Antibiotic Production and Omission-Based Competition:

Probiotic formulations aid in maintaining sound health by various mechanisms, one of the major mechanisms is "competitive exclusion". It involves competition for the available nutrients and reactive sites on the gastrointestinal tissues between probiotic microbes

and pathogens. Probiotics essentially avert the proliferation and colonization of pathogens by saturating the available attachment sites in tissues (15).

Pathogens are inhibited by the production of antimicrobial compounds by probiotic organisms. For instance, bacteriocins, volatile fatty acids (VFAs), H2O2, and diacetyl are among the antimicrobials released by probiotics (16). These biomolecules specifically alter the gut microbiome, creating a vulnerable environment for pathogens while favoring the proliferation of useful microbes. Similarly, VFAs, such as acetate and butyrate, have been known to exhibit anti-inflammatory activity and improve gut barrier function, while inhibiting pathogen colonization (17).

Improving Gut Barrier Function and Immunoregulation:

Probiotic formulations contribute to defenses against foreign elements (pathogens) by strengthening the gastrointestinal barrier. These probiotic formulations enhance the expression transmembrane and adaptor proteins that help in the establishment of a semipermeable barrier in intestinal endothelium and epithelium. This barrier maintains tissue homeostasis and prevents the movement of toxins, undigested foods and pathogens into the vascular system, a condition which is generally referred to as "leaky gut" (18).

Probiotics exhibit immunoregulatory effects and engage with gut-associated lymphoid tissue (GALT) affecting both innate and adaptive immunological responses. These formulations improve host defenses by enhancing antibody production and stimulating immune cells (19). Certain probiotics strains can trigger dendritic cell signaling and alter cytokine secretion, leading to stronger antiviral immunity and diminished inflammation (20).

Neurological and metabolic influences

Recent studies have indicated that probiotics can impact brain function via the gut-brain axis, a network that enables two-way communication between the digestive system and the central nervous system. These useful microbes may have a role in the secretion of neurotransmitters, management of neuro-inflammation, and stress induces responses, which highlights their positive effects on mental health management (21).

While considering metabolomics, probiotic formulations affect energy utilization, nutrient assimilation and insulin responsiveness. Probiotics have been found to influence secretion of secondary metabolites, regulation of bile acid metabolism and management of cholesterol levels. Notably, specific strains such as *Akkermansia muciniphila* have demonstrated potential to manage blood glucose levels and weight by enhancing production of volatile fatty acids and insulin responsiveness (22).

Medical Application: evidence-supported use of probiotic formulations

Gastrointestinal Tract Related Disorders

Probiotic formulations are most widely used and most studied in managing and preventing gastrointestinal tract disorders. Strong data supports their role in lowering the risk of antibiotic-associated diarrhea (AAD), including diarrhea caused by *Clostridiodes difficile* (23). By preserving the equilibrium of gut microbiota during the course of antibiotic treatment, probiotics can reduce the likelihood of AAD by nearly 50% as depicted in meta-analyses (24). In irritable bowel syndrome (IBS), probiotics may have a role in alleviating abdominal discomfort and other symptoms, although the search for more effective strains and formulations is still going on. In case of Inflammatory Bowel Disease, including ulcerative colitis and Crohn's disease, evidence suggests that incorporating probiotics, prebiotics or symbiotic to usual treatment strategies may induce remission especially in ulcerative colitis patients (25).

Role of Probiotics in Metabolic and Cardiovascular Health

Studies have demonstrated that probiotics play a role in improving metabolic wellbeing by managing body weight, blood sugar and lipid levels. Certain strains have been found to be effective in maintaining the body weight, insulin responsiveness, triglyceride levels and preventing hepatic steatosis in animal models exposed to high-fat-diet-induced obesity. Human-studies have demonstrated the positive role of specific probiotic formulations in lowering total and LDL blood cholesterol levels. Nonetheless, extensive research is necessary to identify the most effective strains and their recommended dosage of formulations (26).

Probiotics may offer cardiovascular benefits which might extend to systemic blood pressure management as well as endothelial function improvement apart from just regulating the blood cholesterol levels. Different mechanisms including entero-hepatic metabolism of bile salts, synthesis of biologically active proteins, anti-inflammatory action and modification of gut microbiome, are believed to be responsible for the beneficial effect of probiotics on human heath (27).

Probiotics' role in maintaining Mental Wellbeing and Neurological Activity

Researchers opined that probiotics positively impact

mental health via different signaling mechanisms such as, vagal signaling, immunological modifications, and regulating nervous -endocrine systems 'coordination (10). By lowering the inflammatory responses, managing stress-induced reactions and affecting neurotransmitter synthesis, probiotics could be employed as an effective tool in managing emotional fluctuations. The possibility of employing specific probiotic interventions to avert progression of negativity to major depressive disorder presents a new avenue in the area of psycho-dietetics (28).

Role of Probiotics in immunological reactions

Probiotics play a crucial role in regulating immunological modifications and preventing infections.

Clinical studies have established that certain probiotic strains can improve immunity against pulmonary infections. For example, *Lactobacillus helveticus* GCL1815, has been proven to effectively advert both systemic and common flu symptoms in healthy individuals by boosting antiviral immunological reactions (29). Moreover, probiotics have been used to treat and prevent a number of urogenital tract infections. Certain *Lactobacillus* strains are included in vaginal drug delivery systems to restore the modified vagina-associated microbiome during the course of antibacterial therapy. Probiotics help in maintaining a healthy vaginal environment by modifying the pH levels and preventing the pathogens from proliferating (30).

Safety Standards and Directives for the Use of Probiotics

Regulatory Guidelines and Quality Standards

The regulatory classification of Probiotics differs greatly across nations based on their designated application. For instance, in the United States, Probiotics are classified as dietary supplements, foods or medications depending on their specific use. The majority of the probiotic formulations are marketed as nutritional supplements, which do not need prior FDA approval for commercialization. This directorial system places the responsibility on manufactures to ensure the safety and packaging descriptions of the products, although they are not obligated to disclose effectiveness for particular health claims (31).

The lenient regulatory guidelines have given rise to concerns with quality standards of the probiotics being commercialized. Several studies have reported inconsistencies in the displayed nutritional content and actual nutritional profile of the marketed products. A number of discrepancies were observed even in strain labelling, its effective shelf life and even the proposed cell density present in the probiotic formulations. This lack in detailed representation and labelling about the contents of the marketed probiotics makes it difficult for the customers and medical practitioners to select suitable products. For maintaining the viability and shelf life of the probiotic formulations, it is of utmost importance to store the product under recommended conditions, but generally these storage regulations are neither followed nor communicated to the end-user of any discrepancy (32)

Safety Profiling and Vulnerable Population

Generally, probiotics are found to be safe in fit adults; however, important safety standards should be taken into account when using them in vulnerable populations. Many instances of chronic infections have been documented in preterm infants who were administered probiotic formulations; such incidents have led the U.S. Food and Drug Administration (US FDA) to caution medical practitioners about using probiotic formulations. The populations at risk include immunocompromised patients, people suffering from chronic health conditions, and individuals with conditions like endocarditis. This vulnerable group of people should be wary of using over-the-counter available probiotic formulations without consulting a professional (33).

The ability of microbial strains to cause systemic infections by diffusing or moving across the gastrointestinal barriers in compromised patients is the major risk associated with the probiotic formulations. Another concern lies in the fact that certain probiotic strains possess natural antibacterial resistance genes, and administration of probiotic formulations may lead to horizontal transfer of resistant genes to other pathogenic species. While these risks are negligible for healthy and fit adults, they might be associated with severe repercussions in vulnerable populations (31).

Practical applications of Probiotic Formulations

Medical practitioners and end-users should practice caution while selecting probiotics. Several factors, such as strain exclusivity (strains reported to exhibit intended health benefits), dosage (optimum cell density), viability (recommended storage conditions and due expiration dates), and final product efficacy (selection of certified manufacturing facility), can be considered while procuring probiotic formulations.

The administration schedule may also affect the efficiency of probiotic formulations. It has been observed that initiating probiotics consumption within two days of antibacterial therapy attenuates the antibiotic-associated diarrhea. A few of the formulations are more effective when taken along with meals, while others are more beneficial on having empty stomach. However, consistent intake of these probiotic formulations has been associated with

maintenance of general well-being (9).

New Research Avenues and Future Prospects

Customized Probiotics for targeted patients

Probiotic research is rapidly advancing towards designing customized formulations to address specific microbiota, genomic constitution, and personalized health benefits for a particular end-user. Recent developments in metagenomics, metabolomics, and bioinformatics have enhanced the competency of researchers in identifying microbial footprints linked with illness and sound health, initiating the research to develop targeted probiotic formulations.

It has been found that the particular genetic variations among individuals may influence their responses to biologically active molecules. The study of these interactions is referred to as nutrigenetics, and the way in which certain food molecules affect the genetic expression is referred to as nutrigenomics. Nutrigenetics and nutrigenomics are the major drivers in the development of next-generation targeted probiotic formulations. These strategies might help in designing customized probiotic formulations to address specific individuals' needs (8).

Applications and Innovative Probiotic Formulations

Probiotic research is expanding to new horizons in various medical fields. Current research is focused on investigating the impact of various probiotic formulations for the management of neurological disorders, autoimmune diseases, and other metabolic disorders, including cancer.

Additionally, the use of probiotics presents a potential treatment strategy, complementing conventional treatments, to manage various viral infections and other health concerns (34).

Innovative delivery methods and formulations are being curated to enhance the effectiveness of probiotics. This encompasses miniaturized capsulation techniques, synthetic probiotics (genetically modified) with improved efficacy, and symbiotic blends that are particularly designed to support the proliferation of beneficial strains. Another class of inactive microorganisms or their components, generally referred to as "postbiotics," is also gaining popularity in immunosuppressed individuals, where live probiotic formulations may pose a risk (5).

Conclusion and Futuristic Endeavors

Probiotics have come a long way from being just used as basic fermented foods to being employed as advanced therapeutics in the management of various health conditions. Present-time research endorses the use of probiotics for multiple issues such as gastrointestinal tract-related disorders, antibacterial-induced diarrhea, and irritable bowel. Recent studies indicate possible advantages associated with the use of probiotics formulations for metabolic health, mental wellness, immunity, and skin-related issues, although further research is necessary to establish stringent regulatory guidelines and standards.

Probiotics are typically beneficial for healthy individuals; however, extra care should be taken for the vulnerable population, including pre-term infants and immunosuppressed individuals. Regulatory guidelines and frameworks differ across regions, raising concerns about the reliability of product quality, which further emphasizes the need for caution while choosing a specific probiotic formulation intended for a particular use.

Though research in the field of probiotics has reached new heights, a few research gaps remain that need further exploration. Future research avenues include customized probiotic formulations to address individuals' needs, innovative formulations to improve the efficacy and shelf life of the end product, and wider application in the field of medicine. With the advancement of the knowledge pool in the field of metagenomics and metabolomics, probiotics are considered to play a significant role in preventive healthcare and holistic healthcare practices. Ongoing scientific studies into these microbes are expected to unravel the underlying mechanisms of action and their medicinal properties, further reinforcing their role in overall human well-being.

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Data Availability Declaration

Not applicable, as all the data collected are available in the public domain.

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