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Probiotics: Mechanism of Action, Attributes in the Human Body, Forms in Food and Safety Assessment

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Abstract:

Probiotics, defined as live microorganisms that confer health benefits, have attracted significant attention. Recent advances have demonstrated their effectiveness in inhibiting intestinal pathogens, boosting immune responses, improving oxidative stress in type 2 diabetes, and promoting oral health. Probiotic applications have also expanded into various food forms, such as fermented foods, dairy food, meat food, and so on. Despite these advancements, gaps remain in understanding the safety and efficacy of probiotics. This article delved into the health benefits of probiotics in the human body, and their uses in food. It further evaluated the safety aspects, highlighting the need to address these concerns. This study was noteworthy as it examined methods to improve the efficacy of probiotics in medicine and food applications. With the growing demand for probiotics, it is crucial to ensure their stability and safety. This research provides important insights into improving the integration of probiotics in various products, paving the way for enhanced health benefits and advancements in product development. However, the study has limitations, including a lack of long-term probiotic-host microbiota interaction analysis and insufficient coverage of probiotic regulations. Future research should focus on long-term effects and safety protocols to maximize health benefits and ensure safety.

Keywords: Probiotics; healthy attributes; food; safety assessment.

1. Introduction

Probiotics are nonpathogenic microorganisms comprised of *Saccharomyces boulardii* yeast or lactic acid bacteria (LAB), including *Lactobacillus* and *Bifidobacterium* species [1]. Probiotics were described by Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as “live microbes when administered in adequate quantities, confer health benefits on host organisms”. Initially, Henry

Tissier recommended administering a live organism (*bifidobacterium*) orally to patients with diarrhea (infantile diarrhea) and helping to restore a healthy gut flora. Over the past two decades, the field of probiotics research has advanced significantly, achieving notable progress in selecting and characterizing specific probiotic strains, as well as uncovering the substantial health benefits that arise from their consumption.

Probiotics have been proven to be conducive to human health as medicine treatment, with distinguished suppressive effects against a range of prevalent intestinal pathogens, the release of various cytokines to enhance non-specific cellular immune responses, improvement of oxidative stress in patients with type 2 diabetes, and prevention of the adhesion of pathogenic bacteria on tooth leading to oral health protection [2]. Through these three main mechanisms—pathogen clearance through competition enhances intestinal barrier function, immunological modulation, and host neurotransmitter production—probiotics may have beneficial effects on the human body.

Probiotics usually are manifested in many forms of food items. They are commonly used in many different foods, including pickles and fermented soy products, dairy goods including yogurt and cheese, fruit and vegetable juices, flavorings, and various meat, cereal, and snack items [3]. Owing to probiotics' application in people's medicine treatment and food, safety assessment has become a significant aspect that cannot be ignored, which humans need to pay attention to.

Given the multiple benefits of probiotics in promoting human health, it is important to further study their application mechanism, attributes properties for humans, and safety assessment in use. This not only potentially helps to optimize the formulation and production process of probiotic products, and improve the effectiveness and safety of products, but also may provide humans with more scientific and reasonable health guidance.

This study mainly focused on the health strengths of probiotics in the human body, their applications in food, and evaluation of the safety aspects related to the utilization of probiotics, aiming to provide the theoretical basis for the scientific application of probiotics and promote the healthy development of the probiotics industry.

2. Mechanism and Attributes of Probiotics in Human

Probiotics, as microorganisms that confer health benefits upon their host, exhibit a multifaceted mechanism and possess a diverse array of attributes that contribute significantly to human health and well-being.

2.1 Effect on Gastrointestinal Tract

Probiotics are crucial in the management of diarrhea, especially in mitigating antibiotic-associated diarrhea (AAD) and acute diarrhea in pediatric patients. The analysis of the five incidence rates of AAD using the intention-to-treat (ITT) method, which involves examining all patients as they were randomized, revealed clear advantages of probiotics overactive, placebo, or untreated controls. Also, Higuchi and colleagues' meta-analysis of 14 trials found that probiotics obviously reduced diarrhea duration and hospital stays in children with acute gastroenteritis in Japan [4]. In addition, probiotics are found to be beneficial in relieving chemotherapy-induced diarrhea. Many cancer patients have to be dependent on chemotherapy to inhibit cancer development, but following the side effects such as diarrhea. Studies showed that probiotics can lessen chemotherapy-induced diarrhea of several types of cancer. For example, probiotic supplements alleviated grade 3 diarrhea in advanced breast cancer patients treated with capecitabine and lapatinib, reduced the overall incidence of diarrhea in colorectal cancer patients receiving irinotecan-based treatment and decreased the incidence rates of CID in lung cancer patients taking *Clostridium butyricum* tablets [5].

Additionally, probiotics show promise in the management of functional dyspepsia (FD). FD is a chronic, non-organic gastrointestinal illness that ranks among the most prevalent gut-brain inflammatory disorders globally as well as digestive system disorders. Probiotics (*Bacillus coagulans* MY01 and *Bacillus subtilis* MY02) significantly ($p < 0.05$) improved quality of life, boosted SCFA levels, and decreased symptoms in 68 FD patients, according to Wauter's 16-week research. Furthermore, Sun et al.'s experiment revealed that 26 patients' FD symptoms considerably improved, including less stomach discomfort and hiccups, after taking a beverage containing *Lactobacillus paracasei* LC-37 for 14 and 28 days. While harmful microbes declined, beneficial bacteria rose [6].

It is widely accepted probiotics mainly treat these symptoms through two mechanisms, reinforcing the gut mucosal barrier and regulating intestinal flora. Some probiotics have been shown to enhance the ability to regulate intestinal mucosal immunity by increasing the expression of mucin, and then enhance the immune intestinal barrier, and play an antibacterial role by inhibiting the adhesion of pathogens. The use of probiotics has been scientifically proven to effectively regulate and restore the balance of the microbiome in the gut. In the face of major disease challenges, such as long-term antibiotic treatment, intense physical stress, or the invasion of chronic diseases, the human gut microbiome may become unbalanced. This

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would result in a major decrease in the number of good bacteria that initially help in digestion, including *Lactobacillus* species, *E. coli*, *Bifidobacterium* species, and *Bacillus* spp [7], resulting in diarrhea and other problems. Probiotics are able to break down complex carbohydrates and produce beneficial substances such as lactic acid and short-chain fatty acids. These products not only help to reduce the invasion of harmful bacteria but also effectively help the gut microbiota restore its original state of balance, thereby protecting intestinal health and reducing the occurrence of diseases such as diarrhea and FD.

2.2 Cancer Combat of Probiotics

Many research studies have consistently demonstrated the crucial role that probiotics play in combating cancer. Probiotics exhibit profound positive impacts in modulating immune responses, thus exhibiting anticancer effects. They regulate the immune balance by activating macrophages and lymphocytes in the immune system, improving their phagocytosis capacity, and promoting the production of antibodies and cytokines by monocytes. Furthermore, probiotics stimulate immune cells imbued with anti-inflammatory properties, including dendritic cells (DC) and natural killer cells (NK), thereby amplifying the efficacy of immune regulation. According to studies, long-term ingestion of *Lactobacillus casei* can markedly enhance the activity of NK cells. Concurrently, probiotics meticulously modulate the expression patterns of toll-like receptors (TLR), quell inflammatory responses, sustain T helper cell homeostasis, and activate DC cells, thereby offering robust reinforcement for the comprehensive optimization of the immune system, thereby enhancing anticancer effects [8].

Many studies have consistently demonstrated the advantageous properties of probiotics in regulating the proliferation and apoptosis of cancer cells. Specifically, *L. casei* ATCC393 and its bioactive components have been empirically validated to exert potent anti-proliferative, growth-inhibitory, and apoptosis-inducing effects. Simultaneously, probiotic metabolites, especially short-chain fatty acids (SCFA) like butyric acid, demonstrate a marked regulatory effect on cancer cell division and death. Butyric acid is a valuable prospective therapeutic target since it balances colon cell proliferation and apoptosis. This has been shown by the fact that butyric acid levels are reduced in patients with colorectal cancer [9]. Probiotics not only stop the progression of infections by increasing the synthesis of SCFA, but they also open up new possibilities for cancer treatment.

For breast cancer, probiotics like *Streptococcus thermophilus* generate antioxidants that mitigate DNA damage, whereas LAB possesses the capability to decompose carcinogens. For instance, *Lactobacillus crispatus* and *Lactobacillus acidophilus*, have anti-proliferative activity against breast cancer cells and attenuate transcriptional activity of related antigens through epigenetic regulation. Clinical studies have shown that regular consumption of the probiotic *Lactobacillus casei* white field is significantly associated with a diminished risk of breast cancer [10].

In the prevention and treatment of cervical cancer, probiotics play a role by influencing microbial communities, degrading carcinogens, reducing inflammation, and obstructing the generation of carcinogenic compounds. Probiotic metabolites enhance host cell function by stimulating G-protein-coupled receptors (GPCRs), regulating cytokine production, and thwarting carcinogenesis and local inflammation. Additionally, probiotics contribute to a favorable cervical microbiota environment by adhering to genital mucosa and disrupting biofilm formation, thus preventing HPV infection and cervical cancer. Probiotics such as *Lactobacillus* spp. can prevent cervical cancer metastasis by controlling e-cadherin, altering the cell cycle, modulating cancer-related biomarker signaling pathways, and exhibiting potent anticancer activity [11].

2.3 Intervention of Cardiovascular Disease (CVD)

CVD includes coronary arrhythmias, stroke, hypertension, venous thrombosis, heart disease, cardiomyopathy, artery disease, and thromboembolic illnesses. CVD is a rapidly increasing global health concern. For the previous 15 years, CVD has been the primary cause of death in developing countries, and by 2030, it will claim the lives of almost 20 million people yearly [12]. Probiotics have a certain therapeutic effect on cardiovascular predisposing factors, especially high blood pressure and high cholesterol.

Hypertension serves as a contributing factor that increases the risk of developing CVD. Probiotics, through their metabolites, can effectively regulate blood pressure. For instance, SCFAs activate receptors such as Gpr41 and Olfr78, which subsequently modulate blood pressure via vasodilators and angiotensin. CVD development is linked to oxidative stress. This condition is caused by an increase in oxygen free radicals within cells, which damages DNA, lipids, and proteins. Among the most potent free radicals are reactive oxygen species (ROS), which include hydrogen peroxide, superoxide anion radicals, and hydroxyl radicals. Increases in ROS activity in hypertension patients can cause vascular damage through endothelial dysfunction, lipid oxidation, smooth muscle cell proliferation, and other symptoms. Numerous studies have demonstrated the noteworthy antioxidant activity of probiotics. ROS may originate outside or inside, have high reactivity, and can alter lipids, proteins, DNA, and other forms of oxygen. In spontaneously hypertensive rats, Gomez-Guzman et al. suggested that probiotic fermentation of *Lactobacillus coryniformis* CECT5711 (K8), *Lactobacillus gasseri* CECT5714 (LC9) (1:1) and *Lactobacillus fermentum* CECT5716, could decrease NOX activity and mRNA expression of NOX-1 and NOX-4 [12].

High cholesterol is another risk factor for CVD. Many hypotheses have been proposed about the mechanism of probiotics to reduce cholesterol levels. Among them, the most well-studied mechanism is closely related to bile salt hydrolase (BSH) activity, which facilitates bile dissociation, enhances the release of free bile acids, and diminishes their reabsorption, thereby reducing blood cholesterol levels. Furthermore, probiotics engage in cholesterol metabolism regulation through cell surface binding, incorporation into cell membranes, and the production of SCFAs. It is worth noting that in the presence of bile salts, probiotics can more effectively promote the co-precipitation of cholesterol and free bile acids, which is particularly significant in acidic environments, further bolstering the clearance effect of cholesterol. In the presence of bile salts, potential probiotic strains of *Bacillus campylobacter* and *Bacillus licheniformis* exhibited heightened cholesterol-removing efficacy (27.57-31.22%) (18.48-19.68%) than in the absence of bile salts. Additionally, probiotics possess the capability to absorb and assimilate cholesterol, a mechanism that is crucial in minimizing intestinal cholesterol absorption and subsequently lowering serum cholesterol levels. Probiotic isolates of LAB from a variety of different sources have been reported to have excellent cholesterol assimilation abilities (76.7% to 82.1%) [13].

3. Probiotics in Food

With the growing requirement for functional food, probiotics have become an essential component in many food products, from traditionally fermented foods to advanced formulations like microencapsulated probiotics and probiotics within edible food coating.

3.1 Fermented Food

In general, fermented foods are foods or drinks that are made by regulating the growth of microorganisms and enzymatically transforming food ingredients. Common fermented foods rich in probiotics include yogurt, kefir, miso, natto, kimchi, and sauerkraut. They are of great benefit to human health: The metabolic activity of LAB found in fermented foods is active within the gastrointestinal tract, and even a brief period of colonization can be sufficient for them to produce bioactive compounds, hinder the growth of intestinal pathogens, and facilitate epithelial regulation (such as through interactions with toll-like receptors 149) [14]. This beneficial interaction is further strengthened by the regular daily consumption of fermented foods. Fermented foods additionally exert an influence on the composition of the gut microbiome, which can stem from alterations in the viable (or inactivated) probiotics like LAB present in these foods, as well as the nutrients and metabolites that are liberated through the fermentation process. Furthermore, the host immune system is influenced by these food components, contributing to the overall regulation of the gut microbiota.

3.2 Probiotics Microencapsulated Food

Microencapsulation refers to the physicochemical process of trapping active compounds or cells in a material to improve their function. By embedding probiotics in microgels or other types of microcapsules, the vitality of probiotics can be improved. Carrier particles can be designed in three forms to help probiotics improve their activity. Firstly, microencapsulation technology can be designed to create a physical barrier that shields probiotics from the harsh conditions of the gastrointestinal tract, including stomach acid, bile salts, and digestive enzymes. Secondly, it enables the co-encapsulation of probiotics with essential nutrients, such as digestible carbohydrates, dietary fiber, proteins, lipids, and minerals, which bolster their survival rates. Thirdly, these microcapsules may also incorporate antacids to regulate the pH levels within, further enhancing the stability and viability of the encapsulated probiotics [15]. The application of microencapsulated probiotics in food products has a wide range, such as dairy products, functional drinks, and snacks. The widespread utilization of microencapsulated probiotics in food products ensures their sustained activity throughout the processing and storage phases.

3.3 Probiotics in Edible Food Coatings

Thin layers of edible material are used as edible food coatings to prolong the shelf life and stop food from spoiling. In order to help probiotics overcome the stability and GIT stresses they experience, encasing them in edible films can shield them from early deterioration and increase their viability in the human body. Food coatings containing probiotics can not only preserve food but also provide health benefits through probiotics. There are many different methods and materials for making probiotic-infused food coatings, and common coating materials include polysaccharides (e.g., alginate, chitosan), proteins (e.g., gelatin, whey protein), and lipids, which all can be used to capture

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probiotics to enhance the nutritional value of food.

4. Safety Assessment of Probiotics in Use

Probiotics possess many attributes in treatment for many diseases like gastrointestinal disease, cancer, cardiovascular disease, and so on. Also, there are existing various forms of food, that can provide benefits for humans. However, the safety of probiotics rarely seems to be the focus of research.

Numerous medical research have demonstrated the potential benefits of probiotics in enhancing gut health and the immune system. Although they are usually safe, they can occasionally have unsettling side effects. Bacteremia is one of the most significant theoretical issues with probiotic use in medicine. It was proven by genomic data that the probiotics that were consumed, as opposed to those that colonized the gut, were the cause of these negative effects. The other problem is the negative effect of the intake of probiotics with antibiotics. One study investigated the effects of supplementing with probiotics after antibiotic treatment and found that probiotics disrupted rather than helped the microbiota return to baseline. Antibiotic treatment significantly enhanced the colonization of the intestinal mucosa by probiotics, which then delayed local intestinal mucosal reconstruction by up to five months [16].

At the same time, food with probiotics should also be evaluated for safety. Certain microorganisms, such as those belonging to the LAB, which are associated with long-ripened cheese, sausage, and other fermented foods, possess the capability to harbor transmissible antibiotic resistance genes. Additionally, by the decarboxylation of amino acids, some LAB creates histamine, tyramine, and other biogenic amines during the fermentation process of cheese, meats, vegetables, soybeans, and wine. When a host-mediated detoxification mechanism isn't present, these amines can have moderate to severe side effects, such as migraines [14].

5. Conclusion

This study provided an extensive analysis of probiotics' role in health benefits, including improved gut health and protection against diseases such as cancer and cardiovascular disease. Also, applications of probiotics in food were focused on, covering fermented foods, microencapsulated probiotics, and edible coatings. And safety of the probiotics was also assessed in medicine and food use.

The significance of this study lies in its examination of how to contribute to optimizing probiotic function in clinical medicine and food. As the demand for probiotics continues to rise, ensuring the stability and safety of probiotics becomes essential. This work contributes valuable insights into how probiotics can be better integrated into probiotics products, offering potential pathways for both health benefits and product development.

However, the study does have some limitations. It didn't fully explore the interaction between probiotics and the host microbiota over long periods, which remains a critical area for future investigation. Additionally, the regulatory frameworks surrounding probiotic use in food products require further standardization, which was not extensively covered in this work.

Future studies should investigate these identified gaps more thoroughly, concentrating on clarifying the long-term impacts of probiotic use on human health, while also enhancing and fortifying safety evaluation processes to assure optimal consumer well-being.

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