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IMMUNOMODULATORY CHARACTERISTICS OF PROBIOTICS: MECHANISMS, APPLICATIONS, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Fermented functional food products are one of the key segments of food processing industry. fermentation helps to improve organoleptic properties of food, increases shelf life and produces health beneficial bioactivecompounds. Traditionally, the fermented micronutrients have been considered the main substrate but recent study clarifies that secondary metabolites like polyphenols are emerging to ferment effectively as a substrate. However, polyphenol have long been known as antimicrobial agents, but growing scientific evidences shows that they exert selective effect on bacterial communities whereas they suppress the growth of pathogenic microorganisms, but they promotes the growth, survival and metabolic activity of probiotic bacteria such as Lactobacillus rhamnosus GG. In contrast, probiotic bacteria not only remain alive in polyphenol rich plant or vegetable extracts, rather they starts the probiotification based fermentation, that improves the bioavailability, produces new bioactive metabolites, enhancement of total polyphenol content as well as immunomodulatory and functional properties are significantly

increased. Furthermore, selective probiotic fermentation or probiotic fortification of polyphenol-rich plant and vegetable extracts paves the way for the development of new functional foods and bioactive formulations for pharmaceutical, food, and agricultural applications. This narrative review specifically focuses on the potential for enhancing the immunomodulatory and functional potential of plant/vegetable extracts through Lactobacillus or lactic acid bacteria based probiotification, and highlights the emerging bidirectional relationship between probiotic bacteria and polyphenols.

KEYWORDS: Probiotification, Polyphenols, Lactic acid bacteria, Immunomodulation, Functional foods.

INTRODUCTION

When given in the right doses, probiotics live microorganisms benefit their hosts' health.[1] Probiotics affect people both directly and indirectly by producing bioactive metabolites via changing the gut microbiome's makeup.[2] The use of probiotics has been extensively discussed in the food, pharmaceutical, and medical industries for many years, and because microorganisms offer health benefits, the consumption of probiotic products keeps rising.[3] Probiotics are non-pathogenic microbes that provide health advantages to their hosts when given in appropriate proportions. They are also finding new uses, particularly in the food business. They are used as a supplement to strengthen the immune system and avoid hypertension, hypercholesterolemia, cancer and gastrointestinal diseases by controlling the gut microbiota through diet.[4] Additionally, probiotic substances have grown in importance as functional foods and are thought to be potential microorganisms with health-promoting properties.[5] Probiotics are mostly consumed through dairy or non-dairy products including yogurt and ice cream, as well as food, drinks, and supplements.[6] Alternatively, to increase bioactivity, the active bacteria in fermented foods share genetic similarities with probiotic strains.[7] The process of identifying a safe probiotic species involves assessing its efficacy and safety, if it has been used for a long time with a track record of safety, whether it has been demonstrated to be safe by clinical trials, whether it is genetically stable, whether it has the potential to induce toxicity and side effects, and whether a certain production technique guarantees its safety.[8,9] Bifidobacterium bifidum, B. Infantis, B. Lactis, Saccharomyces bourlardii, Propionibacterium freudenreichii, Lactobacillus acidophilus, Lactobacillus Casei, Lactobacillus Plantarum, Lactobacillus Paracasei, Lactobacillus Johnsonii, Lactobacillus Rhamnosus, Lactobacillus Reuteri, and generally the probiotic species used by humans.[10]

These probiotics have a great masking effect, boost immunity against irritants, treat infections, alleviate colitis and irritable bowel syndrome symptoms, prevent colon cancer, and aid in the prevention of obesity.[11] The nutrition business currently relies heavily on a number of neo-biotic supplements or nutraceuticals, which are different from the probiotics that are often found in fermented foods. In many nations, fermented foods are a staple diet and are distinguished by their effective preparation. It has been demonstrated that the probiotics consumed through them affect vagal nerve activity in the microbiome–gut–brain axis.[12] By converting polypeptides into amino acids, fermentation can increase the body's ability to digest proteins and carbohydrates.[13,14] The lactic acid bacteria (LAB) species are high producers of vitamins and antioxidants that are found in fermented foods.

Probiotics' Immunomodulatory Characteristics

Probiotics are unique, non-pathogenic bacteria that improve health when given to the host in sufficient quantities,[15] helping to maintain of homeostasis in the gut microbiota.[16] They are regarded as one of the best choices for treating infections brought on by invasive viruses or bacteria that are resistant to antibiotics[17,18] and restoring microbial diversity.[19] Nevertheless, the exact chemical processes by which they provide their beneficial benefits remain unclear.[20] Probiotic bacteria have an impact on immunity through a variety of mechanisms, including epithelial colonization with concurrent mucin secretion induction,[19] production of multiple bioactive compounds,[17] competitive exclusion of pathogens by preventing their adherence on the intestinal epithelial surface,[18] and inhibition of pathogen proliferation through competition for vital nutrients.[21,16,22] The release of cytokines and chemokines from immune cells,[23] the activation of TLRs,[21,24] or the suppression of the nuclear factor-κB (NF-κB) pathway[25,26] are the main causes of probiotics' immunomodulatory effects, which differ from person to person. By secreting cytokines and AMPs, probiotics also regulate the JAK/STAT and mitogen-activated protein kinase (MAPK) signaling pathways, which enhances the mucosal and systemic immuneresponse.[25,27] It is well known that probiotic cellular fragments or surface molecules can increase the phagocytic ability of DCs and macrophages[28,29] while also boosting the cytotoxic activity of CD8+ T cells[30] and NK cells.[31,32] Probiotics have been shown to be important in promoting the development and maturation of adaptive immunity cells by modifying innate immune cells.[33,34] Probiotics cause cytokines to be secreted upon adhesion to the IECs, which activates Tregs, which are important mediators in preserving gut homeostasis.[21,35,36] Tregs may reduce inflammatory responses[35] and promote immunological tolerance to commensal

microorganisms[21,36] by producing more interleukin (IL)-10, an anti-inflammatory cytokine, at the expense of pro-inflammatory cytokines in the colonic mucosa. Probiotics encourage a transition from Th2 to Th1 cells in order to limit allergic reactions and manage autoimmune illnesses.[35,18] This is relevant to the necessary balance of T cell subtypes for the appropriate operation of gut immunity.[37] Additionally, probiotics' connection with IECs causes DCs to mature and Tregs to be induced, which encourages mature B cells in Peyer's patches to alter their immunoglobulin type to secretory IgA.[38] The secretory IgA is important for maintaining the integrity of the mucosal barrier, neutralizing bacterial toxins on the mucous membrane, and preventing pathogens from interacting with epithelial receptors.[39,40]

Mechanism of Probiotics

Probiotics are like these tiny living organisms that actually do some good stuff for us when we take them in the right amounts. They work their magic by helping to keep the balance of good bacteria in our guts and overall support our health.[41] One cool thing they do is this competitive exclusion thing where they basically outcompete the bad bacteria for space and resources in our intestines. Another key way probiotics work is by producing antimicrobial substances like lactic acid, hydrogen peroxide, and bacteriocins. These substances help keep the gut healthy by lowering its acidity and stopping harmful bacteria from growing.[42] Probiotics also help strengthen the gut barrier by tightening the cell connections and boosting mucus production, which shields the gut lining from invaders. Moreover, probiotics also have a way of working with our immune cells in the gut. This interaction happens in a special place called the gut-associated lymphoid tissue (GALT). What's interesting is that probiotics can actually boost the production of immunoglobulin A (IgA) and help in controlling how our body responds to certain proteins called cytokines.[43]

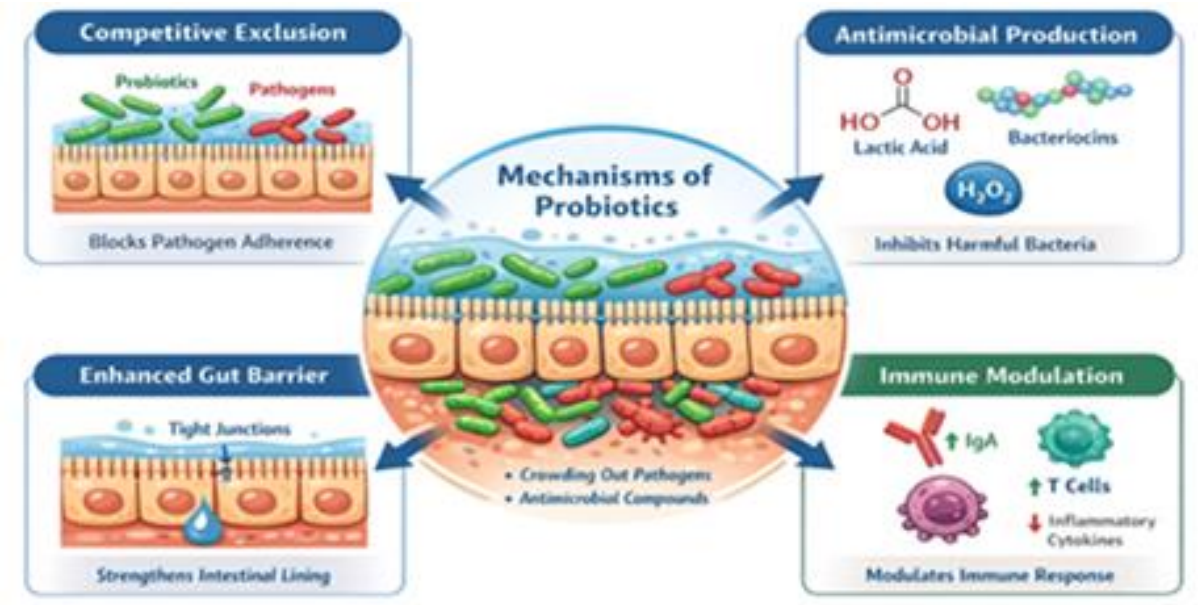

Fig. 1: Mechanism of Probiotics.

Applications

1. Gastrointestinal Health

Probiotics are commonly used to keep our tummies in good shape. They work by balancing out the good and bad bacteria in our gut and stopping harmful germs from growing. Some types like Lactobacillus and Bifidobacterium can help ease diarrhea, even the kind caused by antibiotics or infections.[44]

2. Immune System Modulation

Probiotics are really important for keeping our immune system in check. They help boost our body's natural defense mechanisms by kicking our macrophages into gear, ramping up immunoglobulin production, and keeping cytokine levels in check. Some probiotic strains are great at fighting inflammation and making sure our immune responses stay strong and healthy.[45]

3. Prevention of Allergies

Studies have shown that probiotics can reduce the risk of allergic diseases such as eczema and food allergies. They influence immune tolerance by regulating T-cell responses and decreasing inflammatory reactions associated with allergies.[46]

4. Role in Metabolic Disorders

Probiotics are getting a lot of attention these days for how they can help with metabolic issues like obesity, diabetes, and high cholesterol. They can affect how your body handles fats,

make insulin work better, and lower overall inflammation. Some specific types of probiotics can change the balance of bacteria in your gut and play a role in managing weight.[47]

5. Applications in Functional Foods

Probiotics are widely incorporated into functional foods such as yogurt, fermented milk, cheese, and dietary supplements. These products provide health benefits beyond basic nutrition by delivering beneficial microorganisms to the human gut.[48]

Common probiotic genera include:

- *Lactobacillus*
- *Bifidobacterium*
- *Saccharomyces*

These microorganisms improve gut microbiota balance and enhance overall health.

6. Antimicrobial Activity

Probiotics produce antimicrobial substances such as bacteriocins, organic acids, and hydrogen peroxide that inhibit the growth of pathogenic bacteria. This property makes them useful in controlling infections and maintaining microbial balance in the gut.[49]

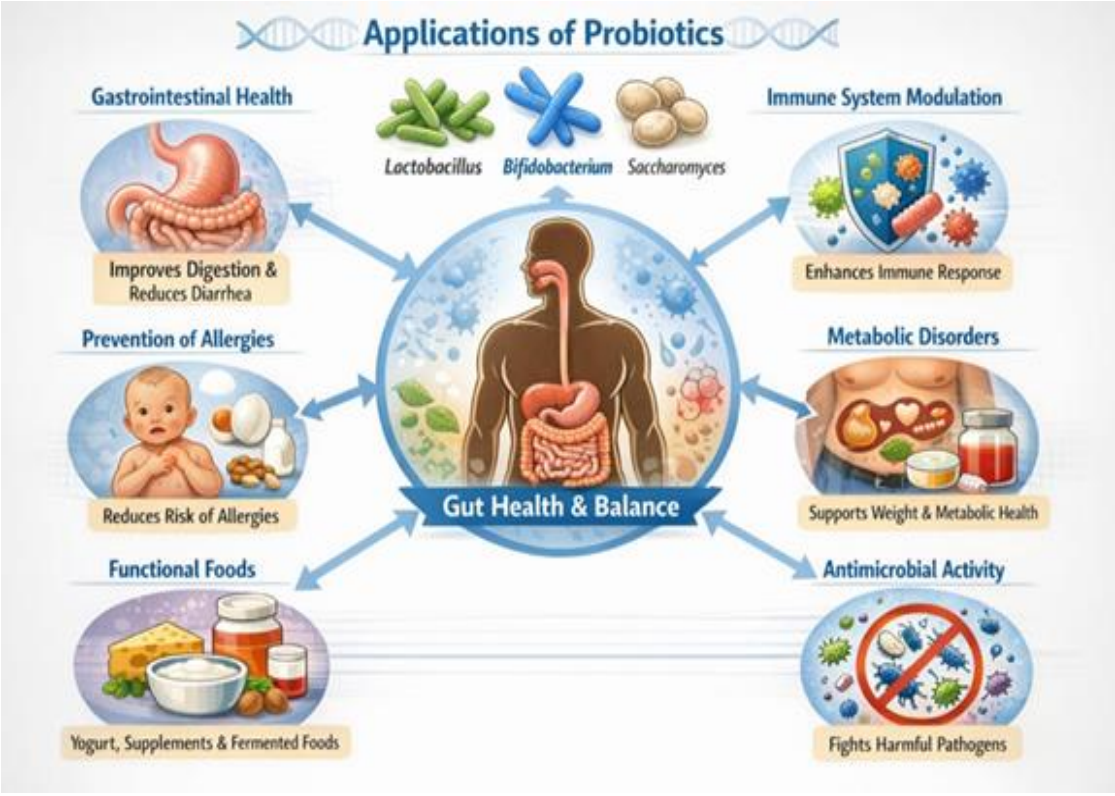

Fig. 2: Application of Probiotics.

Challenges of Probiotics

1. Survival in the Gastrointestinal Tract

One big issue with probiotics is how well they survive the journey through the gut. These helpful microorganisms have to endure tough conditions like stomach acid, enzymes, and bile salts before they can get to the intestine. Unfortunately, many probiotic types don't make it through this process, making them less effective for their intended purpose.[50]

2. Stability During Storage

Maintaining the viability and stability of probiotic strains during storage and processing is another major limitation. Factors such as temperature, oxygen exposure, moisture, and pH can significantly reduce the number of live probiotic cells in food products and supplements.[51]

3. Strain-Specific Effects

The beneficial effects of probiotics are **strain-specific**, meaning that not all strains within the same species produce the same health benefits. This makes it difficult to generalize results and requires extensive research to identify effective strains for specific health conditions.[52]

4. Safety Concerns

Although probiotics are generally considered safe, there are concerns regarding opportunistic infections, antibiotic resistance gene transfer, and immune complications, especially in immunocompromised individuals, infants, and elderly patients.[53]

5. Regulatory Issues

Another challenge is the lack of standardized regulations and guidelines for probiotic products in many countries. Different regulatory authorities classify probiotics as foods, dietary supplements, or therapeutic agents, which creates difficulties in product approval and health claim validation.[54]

6. Limited Clinical Evidence

Although many health benefits of probiotics have been reported, strong clinical evidence is still limited for several applications. Many studies are conducted in small populations or experimental models, which makes it difficult to draw definitive conclusions about their therapeutic effectiveness.[55]

Future Perspectives of Probiotics

1. Development of Next-Generation Probiotics

Researchers are now looking into next-generation probiotics (NGPs), which are essentially newly discovered beneficial microbes found in the human microbiome. These strains are under examination for their potential in treating metabolic disorders, inflammatory diseases, and immune-related conditions. Through advanced technologies like genomics and metagenomics, scientists are able to pinpoint unique probiotic strains with specific therapeutic properties.[56]

2. Personalized Probiotic Therapy

A really cool idea on the horizon is creating personalized probiotics. This means customizing probiotic blends based on a person's gut bacteria, diet, and overall health. Thanks to new technologies like microbiome sequencing and bioinformatics, tailoring probiotics could enhance treatments for gut issues, weight problems, and metabolic conditions.[57]

3. Genetic Engineering and Synthetic Biology

New biotech methods like genetic engineering and synthetic biology are being used to create special probiotic strains. These strains can make helpful substances like medications, germ-fighting peptides, or vitamins right in your gut. These altered probiotics might work as living treatments for different illnesses.[58]

4. Improved Delivery Systems

Researchers are also exploring more advanced methods for delivering probiotics, such as microencapsulation and nanotechnology-based carriers. These methods help shield probiotic cells from harsh stomach conditions and improve their survival and ability to reach their target in the body. By using these technologies, probiotics can become more stable, easier for the body to absorb, and more effective in providing health benefits.[59]

Table: Challenges and Future Perspectives of Probiotics (Summary Table).

Category	Key Aspect	Description
Challenges	Survival in Gastrointestinal Tract	Probiotic microorganisms must tolerate gastric acid, digestive enzymes, and bile salts before reaching the intestine, which can significantly reduce their viability and therapeutic effectiveness.
Challenges	Stability During Storage	Environmental factors including temperature variation, oxygen exposure, moisture, and pH changes may decrease viable probiotic cell counts during storage and processing.

Challenges	StrainnSpecific Effects	Beneficial effects depend on the specific probiotic strain, and strains belonging to the same species may produce different phyological responses
Challenges	Safety Concerns	Possible risks include opportunistic infections, antibiotic resistance gene transfer, and immune complications in vulnerable populations.
Challenges	Regulatory Limitations	Lack of standardized international regulations leads to inconsistent classification of probiotic products as foods, supplements, or therapeutic agents.
Challenges	Limited Clinical Evidence	Many reported probiotic benefits are based on small-scale studies or experimental models, highlighting the need for larger human clinical trials
Future Perspectives	Next Generation Probiotics	Novel beneficial microorganisms identified from the human microbiome are being investigated for applications in metabolic disorders, inflammation, and immune modulation.
Future Perspectives	Personalized Probiotic Therapy	Advances in microbiome sequencing and bioinformatics may enable personalized probiotic formulations tailored to an individual's gut microbiota.
Future Perspectives	Genetic Engineering & Synthetic Biology	Engineered probiotic strains may produce therapeutic molecules such as antimicrobial peptides, vitamins, or bioactive compounds directly in the gut.
Future Perspectives	Advanced Delivery Systems	Technologies such as microencapsulation and nanocarriers can protect probiotics from harsh gastric conditions and improve targeted intestinal delivery
Future Perspectives	Expansion in Functional Foods	Future food innovations are expected to include probiotics in beverages, cereals,plant based foods, and nutraceutical products.

CONCLUSION

Probiotics have increasingly been regarded as playing a vital role in regulating human health and disease due to its effectiveness in conferring novel biological functions. These gut bacteria help in maintaining the balance of gut microbiota, increases the intestinal barrier function and produces antimicrobial compounds including bacteriocins which suppress the growth of pathogenic bacteria. Moreover, probiotics play substantial roles in immune modulation through the activation of immune cells in conjunction with enhanced cytokine responses and immunoglobulin production which help maintain homeostasis of the immune system that acts as a protective mechanism for hosts against infections and inflammatory disorders. Probiotics are health promoting microorganisms which have been extensively used during the last decades especially in the design of functional foods, nutraceuticals and dietary supplements. Their potential benefits as regulators of gut health, attenuators of allergic reactions, and facilitators of metabolic harmony underscore their role in contemporary nutrition and preventative medicine. Additionally, probiotics' functional and immunomodulatory effects are enhanced by their interaction with bioactive substances such

as polyphenols, which gives rise to novel fermented food products. Despite their potential benefits, but several challenges exist such as strain-specific effects, inadequate clinical evidence, gastrointestinal transit survival and regulatory restrictions. Addressing these challenges calls for more high-quality clinical studies and improved delivery technologies to ensure stability and efficacy of probiotics. All in all, probiotics have excellent potential from point of view of food science and medicine and biotechnology. Advancements over the coming years like newest incarnation probiotics, individualized probiotic treatments with novel vehicles will also increase their efficacy and expand their uses in enhancing human health and preventing disease.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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