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A Review on Pharmacokinetics, Mechanism of Action and Side Effects of Probiotics

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Abstract:

Maintaining a healthy balance in the gut flora is essential for a strong immune system. Gut bacteria play a role in regulating the immune system and preventing harmful germs from entering the bloodstream. Controlled experiments have reported that probiotic bacteria are microorganisms that provide health benefits when consumed and offer therapeutic benefits in treating various gastrointestinal disorders, including infectious diarrhea in children, recurrent *Clostridium difficile*-induced colitis, and specific inflammatory bowel diseases. This makes probiotic bacteria a promising therapeutic approach for alleviating human illnesses. While the precise mechanisms governing the communication between microorganisms and the host remain to be fully elucidated, a growing body of evidence suggests that gut bacteria can influence the functioning of the immune system at both a systemic and mucosal level. Recent and noteworthy discoveries indicate that manipulating the microbiota, the collective term for the trillions of microorganisms that live in the gut can exert an influence on the host, revealing novel pathways through which probiotics exhibit their beneficial effects. Additionally, the report delves into the potential adverse effects associated with probiotics, particularly in individuals with compromised immune systems, including instances of fungemia and bacteremia.

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1. INTRODUCTION

Probiotics, also known as beneficial bacteria, provide an approach to deliver components to GIT. These active components include enzymes, such as lactase or sucrase, which aid in digestion, vaccinal epitopes that stimulate immune responses, immunomodulatory constituents that regulate immune system activity, and elements with antagonistic functions that combat harmful microorganisms. Probiotics can serve as carriers for these active components, protecting them from stomach acids and ensuring their delivery to the intended site of action (Adams and Marteau, 1995; Jehan *et al.,* 2019).

Probiotics can influence GIT physiology through both direct and indirect mechanisms (Legan *et al.,* 2022). Understanding their pharmacokinetics is crucial for addressing several key questions: determining the optimal consumption quantity, frequency, and duration of probiotics; establishing correlations between the effects and the probiotic concentration at the target site; validating hypotheses such as the importance of a probiotic's human origin, high survival rate, and adherence to the intestinal epithelium; predicting the effects of alternative probiotics; defining the concentrations required in commercial preparations; and ensuring safety (Marteau and Vesa, 1998).

Determining the optimal quantity of administered probiotic microorganisms is a complex task. It is acknowledged to be strain-specific, contingent on the intended beneficial effect, with different strains and quantities possibly needed for different effects. A significant probiotic microbial population may be required to exert an influence on the composition and metabolic activity of the host microbiota (Ma *et al.,* 2023). Several factors play a role in determining the daily probiotic dosage, encompassing considerations such as the dosing frequency, the timing of meals (before, during, or after), the duration of administration (spanning from 1 day to several months), the delivery method (including fermented foods, beverages, capsules, tablets, or powders), and the viability of the probiotic strain (Lee and Salminen, 2009).

Yogurt bacteria are an example of this. People with hypolactasia, who have trouble digesting lactose, find that the lactase activity from yogurt bacteria reaches the duodenum when they eat yogurt but remains inactive in digesting lactose (Pochart *et al.,* 1989). It is thought that beyond the small bowel, likely due to bile salt lysis of yogurt bacteria, lactase is released, becomes active, and helps lactose digestion (Marteau *et al.,* 1990; Icer *et al.,* 2023).

The hypothesis arises that bacteria like *Lactobacillus acidophilus*, which also have lactase activity, may be less effective than yogurt bacteria in aiding lactose digestion due to their greater resistance to bile, resulting in less efficient release of their intracellular lactase content (Gilliland and Kim, 1984).

Furthermore, distinctions exist between formulations featuring a single probiotic strain and those with multiple strains. However, it remains unclear whether supplementing with combinations is more advantageous than utilizing a solitary strain. Analysis of 16 comparative studies revealed that in 12 cases (75%), probiotic combinations demonstrated greater effectiveness than individual components, though many studies had biased comparisons due to dose variations. The inclusion of diverse Probiotic categories within a multi-strain formulation might potentially reduce efficacy due to mutual inhibition among different species. Nevertheless, data support the notion that mixtures tend to be more effective than single strains, possibly attributed to a higher concentration of probiotics, a broader spectrum of action, and synergistic effects (Chapman *et al*., 2012).

Research indicates that the consumption of commercial probiotics sometimes causes a rise in specific intestinal microflora, although bacterial count in the intestine typically remains unchanged. The impact on animal health is summarized in Figure 1 (Prado *et al.,* 2008). The primary justifications for employing probiotics to prevent and address digestive disorders in animals are:

(i) Their role in maintaining the balance and proliferation of the beneficial microbial population in the gastrointestinal tract, is crucial for "digestive health" (Collado *et al.,* 2007). These supplements have shown the ability to modify the existing intestinal flora, providing an advantage to the host. As previously mentioned, Probiotics can impact the functioning and makeup of the gut microbiota, primarily exerting metabolic effects at particular locations with unique metabolic activities, such as the intestinal region (Quigley, 2010).

(ii) Probiotics help in modulating immunity, particularly inflammatory bowel diseases. Upon colonization in the gut, probiotics trigger an immune response by stimulating intestinal cells to produce various immunoregulatory molecules. This immune response is mediated by peripheral blood mononuclear cells (PBMCs), whose ratios and cytokine production have been shown to influence vaccination responses in piglets (Strompfova *et al.,* 2006). Additionally, studies have demonstrated that *B. cereus* var. toyoi can alter the immune status and functionalities of systemic immune cell populations (Schierack *et al.,* 2007).

(iii) Probiotics may modulate the immune system by altering mucus or chloride secretion or by tight junction proteins in epithelial cells. However, the precise mechanism of this action is still being investigated (Yang *et al.,* 2015). Animals have an adaptable immune system that must be activated in specific situations, such as infections or immune deficiencies while being suppressed in conditions like allergies or autoimmune diseases (Borchers *et al.,* 2009).

Studies demonstrate that resident gut microbiota bolsters an animal's immune defenses against invading pathogens. This protective effect is mediated by the activation of the gastrointestinal immune response, which leads to an increase in antibody production and phagocytic activity (Yirga, 2015; Farooq *et al.,* 2020).

Many pharmacokinetic studies primarily focus on elucidating the fate of probiotics, often referred to as their "survival," within the gastrointestinal tract. In vitro models, such as those assessing adherence to the intestinal epithelium (Elo *et al.,* 1991), can provide insights. Static models offer information on strain sensitivity to fixed pH or bile concentrations (Conway *et al.,* 1987), while multicompartmental dynamic models, driven by computer programs, simulate the dynamics of intestinal chyme transit as well as gastric and biliary secretions (Oak and Jha, 2019). These models aim to more accurately predict in vivo scenarios and study the impact of parameters like concentration of bile or fluctuating acid discharges (Tokatli *et al.,* 2015).

To establish probiotic pharmacokinetics in GIT, in vivo measurement is considered quite effective. Three techniques for obtaining gut lumen samples at different sites include 1) feces or stoma effluent collection, 2) pyxigraphy, and 3) intestinal intubation. Stoma effluent sampling is exclusive to patients. In pyxigraphy, the patient takes in a capsule that can be accessible and contained internally in the GIT lumen (Papadimitriou *et al.,* 2015).

It is imperative to recover the probiotic in excrement before sample collection for examination. As of our knowledge, the technique of using pyxigraphy has not been employed to study probiotic pharmacokinetics. Intestinal intubation stands out as the optimal method for obtaining samples from any part of the gastrointestinal tract (GIT). Perfused techniques, when utilized, enable the determination of both probiotic concentrations and their flow rates (Takada *et al.,* 2020).

When evaluating a probiotic's potential for colonization, indicators become crucial regardless of the GIT sample method used. Our method, like others, uses *Bacillus stearothermophilus* spores as a transit marker. *Saccharomyces boulardii* spores can be readily counted on agar plates at 65°C, an inhospitable temperature for most intestinal bacteria, allowing for accurate quantification. Unlike vegetative cells, these spores remain dormant and are not affected by the harsh conditions of the gastrointestinal tract, passing through the digestive system without replicating or succumbing to destruction. Once consumed, *S. boulardii* spores are eliminated through the feces

in a predictable exponential pattern, disappearing completely within 5 to 9 days in individuals with normal intestinal transit. The use of macroscopic markers, such as plastic pellets, to track the transit of *S. boulardii* is less effective, as these markers fail to capture the significant decline in spore numbers that occurs in the colon, where only 1% of the marker remains present after eight days (Saxelin *et al.,* 2010).

Clinical studies have provided compelling evidence supporting the benefits of probiotics in treating medical conditions, including allergy diseases like atopic dermatitis and gastrointestinal disorders such as irritable bowel syndrome, gastrointestinal infections, *Helicobacter pylori* eradication, inflammatory bowel disease, and diarrhea. Probiotics have also demonstrated efficacy in numerous trials for managing type 2 diabetes, obesity, insulin resistance syndrome, and non-alcoholic fatty liver disease. Additionally, probiotics have been shown to enhance immunity through immunomodulatory effects. Scientific literature also highlights the potential benefits of prophylactic probiotic use in preventing various types of cancer while addressing the associated adverse effects (Figure 1). Recommended probiotic dosages vary depending on the specific condition being treated, acknowledging that probiotic efficacy can be influenced by factors such as strain, dosage, and formulation (Bengmark, 2005; Iqbal, 2019; Iqbal *et al.,* 2019; Kiray *et al.,* 2019).

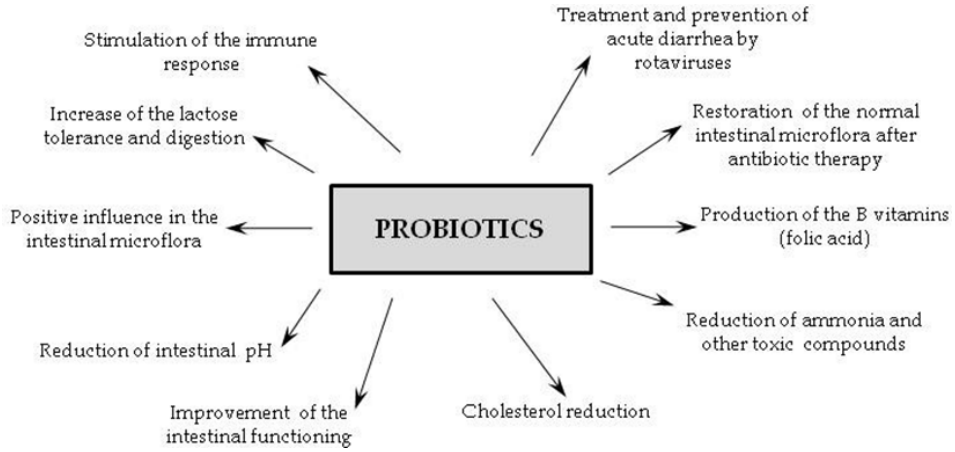

Fig. 1. Probiotics effects on animal health (Prado *et al*., 2008).

2. Probiotics

Humans normally ingest a significant amount of living microorganisms, mostly bacteria, via food and water every day. These microbes are also aided by intentional additions made during food preparation, such as in cheese, yogurt, sausages, and fermented milk products. Because probiotic microorganisms have been shown to improve human health, they have been purposefully added to several meals for decades (Bonifait *et al.,* 2009; Ashraf and Iqbal, 2021).

Probiotics are live microorganisms that confer health benefits to the host when consumed in adequate amounts. This definition was endorsed by FAO and WHO in 2001. Most probiotic strains belong to the *Lactobacillus* and *Bifidobacterium* genera. Since these bacteria can dwell in the human body without harming it and have been essential for food preservation and milk fermentation since ancient times, they are widely regarded as safe (Reid *et al.,* 2003).

Numerous randomized clinical trials have provided health benefits of probiotic strains,

which are now widely employed to benefit consumers. Chronic and transmissible diseases (such as Crohn's disease and acute diarrhea), cardiovascular disease, UTI infections, oropharyngeal infections, carcinoma, food allergies, lactose resistance, fibrosis, reduction of antibiotic-associated side effects, and dental and oral disorders (treatment of oral malodor and dental caries prevention) are just a few of the conditions that these bacteria may be beneficial for. As more advanced research techniques for studying microbe-host interactions become available, this list will only get longer (Gueimonde and Salminen, 2006).

2.1 Criterion for Probiotic Strain Selection

Prominent scientific bodies, including the WHO, FAO, and EFSA have recommended that probiotic strains be selected based on their ability to meet safety, functionality, and technological usefulness standards (Table 1). The probiotic properties of microorganisms are attributed to specific strains within a species, not to the genus or species as a whole (Hill *et al.,* 2014).

The origin of the strain, its lack of interaction with pathogenic cultures, and its profile of antibiotic resistance are among the safety factors. Immunomodulatory effects and survival in the gastrointestinal tract are considered functional features. Probiotic strains also need to meet production-related technological standards so that they can withstand and retain their qualities during the distribution and storage procedures. Furthermore, according to Lee (2009), probiotics should exhibit pro-health effects that have been scientifically proven and align with the traits of the strain used in a product that is sold.

It is stressed that scientific studies and review papers for one strain should not be used as a basis for promoting other strains as probiotics. Moreover, research describing the probiotic qualities of a strain with a measured dose does not indicate that the same strain has the same qualities at a different dose. The kind of carrier/matrix is also important because it can affect a strain's viability and change the product's characteristics (Sanders *et al.,* 2007).

Table 1. Selection criteria for probiotic strain.

Requirement	Properties
Safe use	● Originating from either human or animal resources ● Separated from GIT of people in good health. ● Safe use in the past ● Accurate diagnosis (phenotype and genetic characteristics). ● Lack of information about a connection to infectious diseases ● Lack of bile acid and salt cleaving capacity. ● No negative results. ● Absence of antibiotic resistance genes concentrated in unstable regions.
Functionality	● Competitiveness against the microorganisms that live in the gut environment. ● Ability to tolerate, maintain metabolic activity, and grow inside the designated region ● Intolerance to enzymes and biliary salts. ● Resistance to the acidic pH of the stomach. ● Competition between the microbial species that live in the gut ecology, even those that are closely related. ● Hostile behavior towards pathogens, such as *Salmonella* spp., *Clostridium difficile*, *Listeria monocytogenes*, and *H. pylori*. ● Resistance to the endogenous gut microbiota's production of acids and bacteriocins. ● The capability of microorganisms to adhere to and colonize specific sites within the host organism, coupled with a suitable survival rate in the GIT system.
Technological	● Simple generation of large biomass volumes and excellent culture productivity.

usefulness	● The capacity of probiotic microorganisms to maintain their desirable characteristics when fixing (freezing, freeze-drying), preparing, and distributing probiotic goods ● High rate of product survivability during storage (in aerobic and micro-aerophilic environments). ● Assurance of the final goods' desirable sensory qualities (in the instance of the food sector). ● Stability of genetics. ● Bacteriophage resistance

2.2 Probiotic microorganisms

Several genera of bacteria commonly found in the human gut exhibit probiotic properties, including *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Enterococcus*. Probiotic supplements may include potentially several chosen microbial strains. Furthermore, probiotic products frequently contain strains of *Saccharomyces* yeast and Gram-positive *Bacillus* bacteria (Simon, 2005). General food laws set forth restrictions on probiotics, with a focus on their safety for both human and animal health. The FDA regulates microorganisms for food in the United States. These germs are termed GRAS (generally regarded as safe) (Burdock and Carabin, 2004). EFSA coined the phrase QPS and first used it in Europe and qualified the assumption of safety. A safe usage history and the lack of danger of developing antibiotic defiance are two further safety evaluation factors for bacterial supplements that are incorporated into the QPS concept (Gaggía *et al.,* 2010). Information on probiotic bacteria utilized as food additives and included in medicinal goods is given in Table 2.

Table 2. Human nutrition and probiotic microbes.

Lactobacillus	Bifidobacterium		
L. acidophilus (a),*	*B. adolescentis* (a)	*Enterococcus faecium* (a)	*Bacillus clausii* (a),*
L. amylovorus (b),*	*B. animalis* (a),*	*Lactococcus lactis* (b),*	*Escherichia coli* Nissle 1917(a)
L. casei (a),(b),*	*B. bifidum* (a)	*Streptococcus thermophilus* (a),*	*Saccharomyces cerevisiae* (boulardi) (a),*
L. gasseri (a),*	*B. breve* (b)		
L. helveticus (a),*	*B. infantis* (a)		
L. johnsonii (b),*	*B. longum* (a),*		
L. pentosus (b),*			
L. plantarum (b),*			
L. reuteri (a),*			
L. rhamnosus (a),(b),*			

(a) Generally as pharmaceuticals; (b) generally as additions to food; * QPS (Qualified Presumption of Safety)

2.3 Mechanism of action of probiotics

The recent research on probiotics has made significant strides, especially in the areas of prospective uses, health benefits, and the selection and properties of specific probiotic cultures. Probiotics provide a spectrum of positive impacts on human well-being. One of these benefits is their impact on the formation of the microbiota, which maintains the healthy balance between bacteria and pathogens required for regular physiological function (Oelschlaeger, 2010).

Viable microorganisms meeting the established standards are used to preserve food and

produce useful foods. After receiving antibiotics, their beneficial effects are used to restore the natural microbiota (Johnston *et al.,* 2006). Combating the activity of pathogenic intestinal microbiota that is ingested via contaminated food and the environment is another role. By effectively suppressing the growth of harmful bacteria such as *Yersinia*, *Shigella* species, *Campylobacter jejuni*, *Salmonella enteritidis*, and *Clostridium perfringens*, probiotics can help prevent foodborne illnesses. Additionally, probiotics have been shown to alleviate food allergies, improve digestive processes, combat candida infections, and promote dental health (Thomas and Greer, 2010).

Several probiotic microbes, including *Bifidobacterium adolescentis*, *Lactobacillus plantarum*, *L. reuteri* (Gu *et al.,* 2015), and *B. pseudocatenulatum* (Pompei *et al.,* 2007), possess the natural ability to synthesize vitamin B (B1, B2, B3, B6, B8, B9, and B12). These beneficial microbes help produce organic acids and amino acids, enhance the immune system's efficacy, and promote the absorption of vitamins and minerals (Sanders *et al.,* 2007). Additionally, probiotic microbes exhibit the capability to produce coenzymes A, Q, NAD, and NADP, along with enzymes such as lipase and esterase. Certain byproducts of the metabolism of probiotics have the potential to be immunosuppressive, anti-cancerogenic, and antibiotic (acidophiline, bacitracin, lactacin). It has become possible to determine the foundations of the probiotics' positive effects through molecular and genetic investigations involving four mechanisms (Markowiak and Śliżewska, 2009).

- Antagonistic effects of antimicrobial substances (Cao *et al.,* 2013).
- Nutritional-adhesion competition among pathogens (Schluter *et al.,* 2015).
- Immune system modulation (Forsythe and Binenstock, 2010).
- Inhibition of synthesis of toxins by bacteria (Zhang *et al.,* 2023).

The influence of probiotics on other bacteria is closely linked to the first two mechanisms. These mechanisms are crucial for both treating and preventing infections and maintaining the host's gut microbiota balance. One of the ways in which probiotic strains can create a barrier preventing pathogens from colonizing the epithelium is through co-aggregation (Gomaa, 2013).

Probiotic bacteria can attach to epithelial cells, preventing the adhesion of pathogens, and thereby positively impacting the host's health. Furthermore, adherence of microbes with epithelial cells can initiate a cascade that ultimately leads to immunomodulation. Additionally, the release of specific soluble components can directly or indirectly stimulate immune cells in both treating and preventing infections and chronic gastrointestinal inflammation (Oelschlaeger, 2010).

In vitro studies have shed light on low molecular compounds produced by probiotic bacteria, such as hydrogen peroxide and short-chain fatty acids, in suppressing pathogen growth. Notably, *Lactobacillus* species possess the ability to synthesize bacteriocins, a group of antibiotics encompassing LMWB – antibacterial peptides and class III bacteriocins. Furthermore, research by Jones et al. (2008) has demonstrated that probiotic bacteria like *Lactobacillus* and *Bifidobacterium* can produce deconjugated bile juice, the derivative of bile acids that exhibit antibacterial activity stronger than bile salts made by their host organisms.

Research is warranted to elucidate the mechanisms by which Lactobacillus bacteria develop resistance to their metabolites. Iron, an essential nutrient for most bacteria, is not required by *Lactobacillus* bacteria for survival in their natural environment. However, this adaptation may provide *Lactobacillus* bacteria an edge over other microbes. Through sequestering iron hydroxide on its surface, *Lactobacillus delbrueckii* effectively renders iron unavailable to other microorganisms, thereby hampering their growth and metabolism (Zhu, *et al*., 2014).

The immunomodulatory effects of the gut microbiome, including probiotic bacteria, are

characterized by three seemingly contradictory mechanisms (Chingwaru and Vidmar, 2017).

1. Initiation and maintenance of the immune tolerance state against environmental antigens, including dietary and respiratory components.
2. Immune response induction and modulation against infections.
3. Inhibition of auto-aggressive and allergic reactions.

Probiotic immunity is characterized by enhanced immunoglobulin preparation, elevated activity of lymphocytes and macrophage, and γ-interferon synthesis. Probiotics can influence both the innate and adaptive immune systems through their metabolites, cell wall components, and DNA, which are recognized by specific host cells equipped with receptors (Vonk *et al.,* 2012).

Immune cells in the gastrointestinal tract and intestinal epithelial cells are important host cells that are essential for the immune response. Lactic acid bacteria's cellular wall components activate macrophages, boosting their capacity to swiftly eradicate microorganisms by generating more free oxygen radicals and lysosomal enzymes. Additionally, immunocompetent cells in the gastrointestinal system can be stimulated by probiotic bacteria to produce cytokines (Markowiak and Slizewska, 2017).

On the other hand, yeast's immune activity is associated with glucans in their cellular wall, which activates the reticuloendothelial system's response (Seksik *et al.,* 2008). Probiotics work to limit the generation of bacterial toxins by inducing toxins and aiding in their excretion from the body. According to Nikbakht Nasrabdi et al. (2013), there are two possible ways in which this detoxification process takes place: either through the breakdown of mycotoxins like aflatoxin by microbes, or by adsorption, in which certain strains attach toxins to their cell wall, decreasing intestine absorption.

Consequently, research is required to choose strains capable of such detoxification. Some probiotics' capacity to shield the body from toxins may be related to how well they work against diarrhea. Recent metagenomic studies have shown that the gut microbiota is important for host metabolic functions, such as blood pressure management, glucose metabolism, immunological modulation, and cholesterol absorption regulation (Upadrasta and Madempudi, 2016).

Nutritional programming is a field of continuing attention for the prevention or treatment of metabolic illness symptoms because it aims to manipulate the makeup of the gut microbiota by probiotic delivery. Probiotics may have wider uses in improving health problems related to metabolic disorders like hypertension that are linked to a higher risk of cardiovascular illnesses. This is the subject of the current study. To enhance the overall health state of the host, more research is required to evaluate the targeted and successful usage of varied probiotic strains across various metabolic diseases (Khalesi *et al.,* 2014).

To validate the advantageous function of probiotics in improving cardiovascular health and lowering blood pressure, further comprehensive investigations are necessary to elucidate the fundamental mechanisms of probiotic activity. All of the aforementioned probiotic action mechanisms may work together to protect against cancer, and infections, and to stabilize the gut microbiota of the host. But it is unlikely that anyone probiotic microbe has qualities covering all four areas at once, acting as a cure-all for a variety of illnesses. Probiotic activity is significantly influenced by specific characteristics, including cell structure, area, metabolic characteristics, and secretary compounds. As a biotherapeutic product, the use of probiotics with different modes may provide increased safety. Figure 2 summarizes the mechanisms and effects of probiotic action (Bengmark, 2009).

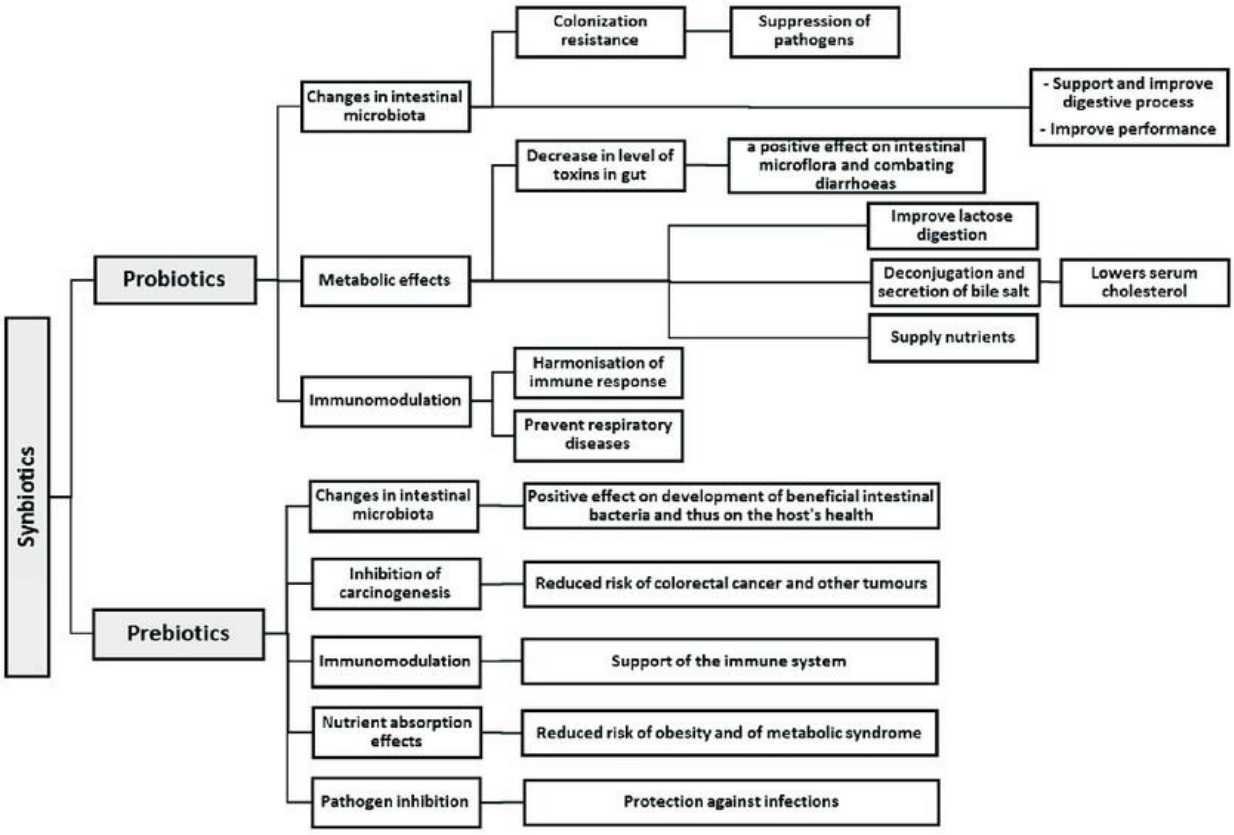

Fig. 2. Mechanism of action of synbiotics and their consequences (Bengmark, 2009).

2.4 Effect of Probiotics on human

In the context of the prevalence of diseases and an aging population, it has become increasingly important to understand the microbiota in the gastrointestinal tract and the beneficial effects of probiotic bacteria. The consumption of highly processed, high-fat, low-vegetable fast food has been linked to detrimental changes in the gut microbiota. Modifying the microorganism system in the intestines through probiotics can help protect against gastrointestinal issues and contribute to overall health improvement (Van Immerseel *et al.,* 2010).

Despite animal studies suggesting that probiotics may lower colorectal cancer risk by inhibiting specific bacterial enzymes, human clinical trials have not conclusively demonstrated this effect (Hunt *et al.,* 2011). Conversely, probiotics have exhibited positive effects on the urogenital system, holding promise for preventing and treating Urinary Tract Infections (UTIs) and bacterial vaginosis (Falagas *et al.,* 2008). Probiotic administration to pregnant women and neonates to prevent diseases has also been explored, though its effectiveness remains a subject of debate (Kuitunen *et al.,* 2009).

Probiotic consumption through dairy products has been linked to a reduction in blood cholesterol levels, diabetes, heart diseases, and strokes. While the cholesterol-lowering effect of

probiotics is less pronounced than that of pharmaceutical agents, it is associated with significantly fewer side effects (Xie *et al.,* 2011).

Probiotics have been extensively investigated for their potential in treating diarrhea. *Saccharomyces boulardii* yeast given to patients who had acute watery diarrhea has demonstrated its effectiveness in achieving a cure and reducing the recurrence of such episodes within the following two months. Probiotic strains have also shown efficacy in treating various types of diarrhea, including nosocomial, non-nosocomial, and viral cases. Probiotics enhance the production of antibodies IgA, potentially contributing to the suppression of infections caused by the virus (Kang *et al.,* 2020).

Antibiotic-associated diarrhea is the side effect of antibiotic treatment, and *Clostridium defficile* disease, triggered because of antibiotics, is a leading cause of diarrhea and colitis upsurges. The use of probiotics for these conditions has been a subject of debate. Meta-analyses have indicated that three probiotic strains—*Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and probiotic mixtures—can significantly reduce the incidence of antibiotic-associated diarrhea. However, only *S. boulardii* has demonstrated efficacy against CDD. Furthermore, studies conducted in a foster home in Helsinki, Finland, revealed that regular consumption of *Lactobacillus rhamnosus* GG as a probiotic resulted in a reduced frequency of respiratory tract infections (McFarland, 2009).

Emerging research suggests that a diet devoid of fermented foods can impair the body's inherent immune response. This reduces Lactobacillus and short-chain fatty acid levels in stool. Moreover, after two weeks on such a diet, a decline in leukocyte phagocytic activity was observed, potentially weakening the body's ability to combat infections (Lampe, 2011).

A randomized, double-blind trial involving 30 healthy participants examined the effects of a product with *L. gasseri* CECT5714 and *L. coryniformis* CECT5711 on fecal and blood samples. The probiotic group experienced no adverse effects and reported positive outcomes such as increased short-chain fatty acid production, improved stool characteristics (frequency, volume, and moisture), and a subjective enhancement of intestinal function. Additionally, Zein et al. (2008) noticed reductions among Enterobacteriaceae counts and enhanced galactosidase activity in consumers compared to non-consumer's alimentary tract (Honeycutt *et al.,* 2007).

It is important to recognize that, just as different probiotic strains are not expected to exhibit identical clinical effects, each probiotic strain, is likely to have a unique safety profile. Moreover, the safety of a commercial probiotic product is not contingent on the probiotic being itself but also on the other components of the product. A report by the World Health Organization and the Food and Agriculture Organization in 2002 stated that "probiotics can be theoretically be associated with following side effects."

1. Infections that are inherent.
2. Metabolic activities that may cause deletions.
3. Immune stimulation in vulnerable beings.
4. Genetic inheritance.

WHO/FAO proposed a comprehensive framework for evaluating the safety of novel probiotic strains. This encompasses testing antibiotic resistance, hemolytic potential, and production of toxins and estimation of metabolic activities i.e. D-lactate production and deconjugation of bile salt. Human studies help evaluate potential side effects, and market surveillance for commercial products crucially. Additionally, conducting studies on probiotic usage in immunocompromised animals can provide valuable insights into their potential infectivity in such hosts. This holistic approach aims to enhance our understanding of the safety profile of probiotics. Here's a summary of the current knowledge regarding each potential adverse event category.

2.5 Systemic infections

Several case reports have documented instances of infection associated with microorganisms closely related strains in individuals who had taken probiotics prior to developing symptoms. Frequent occurrence of fungemia, with more than 33 cases where *S. cerevisiae* or *S. boulardii* (microbiologically indistinguishable organisms) were identified in the blood of patients who consumed the probiotic *S. boulardii* (Lolis *et al.,* 2008). Additionally, eight documented cases of bacteremia have been reported, involving various *Lactobacilli* strains such as *Lactobacillus acidophilus* and *Lactobacillus casei* (Santino *et al.,* 2014).

A detailed 6-year study in Sweden coincided with the increasing consumption of three commercial probiotic *Lactobacillus* strains. Despite this surge in probiotic use, no incidence of lactobacillemia was observed, and no cases of *Lactobacillus* taken from the blood samples could be attributed to the probiotic strains (Ouwehand *et al*., 2004).

A significant safety concern regarding probiotics arose from a clinical trial conducted by Besselink et al. (2009). This placebo-controlled randomized trial evaluates the effectiveness of a multi-strain probiotic in preventing infections in 296 cases with severe pancreatitis. However, the group that received probiotics exhibited a greater mortality rate. To explain this unexpected outcome, the authors proposed two potential mechanisms: more oxygen required in the gut mucosa by probiotic administration, particularly under reduced conditions, blood flow, or an inflammatory reaction in the small bowel triggered by probiotics, leading to a reduction in capillary blood flow.

2.6 Excessive immune stimulation in susceptible individuals

Due to the demonstrated effects of probiotics on both the innate and adaptive immune systems, including the modulation of cytokine secretion and dendritic cell function (Braat *et al.,* 2004), there is a theoretical concern about the possibility of excessive immune activation in certain individuals. This could potentially lead to autoimmune reactions or inflammation. However, it is important to note that, to date, there is no documented evidence of these theoretical concerns manifesting in human subjects.

2.7 Gene transfer

Because of the presence of these epizootic cells, many antibiotics are not effective against lactobacilli bacteria. There is evidence that Leukobacillus species and Pedioccocc species may inherit broad-host-range antibiotic-resistant plasmids (BLDRs) from Lactoccus species. Although transfer to enterococci can take place in the intestinal tract of animals and laboratory settings, transfer to Lactobacilli has been observed to be relatively rare. Molecular assays for the identification of the Vancomycin-resistant gene of *Lactobacillus* are inconclusive, as no Van A,B,H,X,Z,Y, or S were identified by hybridization or PCR products (Johnston *et al.,* 2012). While there is a theoretical risk that probiotic microorganisms may pass horizontal genes to other gut microbes, there is no clinical evidence to support the transmission of AMR. This is especially important because probiotics are used in combination with antibiotics.

2.8 Gastrointestinal side effects

Studies have documented mild gastrointestinal symptoms in people taking probiotics, such as abdominal cramps, nausea, loose stools, gas, and taste changes. However, a meta-analysis and systematic review for the prevention of *Clostridium difficile*-associated diarrhea (CDAD) showed that patients treated with probiotics had fewer (about 18%) of these side effects compared to control subjects up to 20%) (Goldenberg *et al.,* 2017).

2.9 Effect of probiotic translocation on immunocompromised individuals

Safety of probiotic translocation in healthy individuals is generally considered safe, but studies involving individuals with underlying health conditions suggest a different scenario. In healthy individuals, the mesenteric lymph nodes

effectively trap and eliminate bacteria, providing a protective barrier. However, this protective mechanism may be compromised in immunocompromised patients. Additionally, prolonged or high-dose antibiotic administration before an infection can alter the gut microbiome, potentially leading to the selection of antibiotic-resistant strains. These resistant strains may then outcompete other enteric bacteria and facilitate bacterial translocation (Cannon *et al.,* 2005).

Research suggests that different strains of probiotic bacteria may influence patterns of translocation in varying ways (Rodriguez *et al.,* 2001). Clinical reports have implicated certain Lactobacilli strains as potential contributors to conditions such as dental caries, urinary tract infections, chorioamnionitis, endometritis, meningitis, intra-abdominal infections, and liver and spleen abscess formation. Typically, these infections are associated with pre-existing conditions, such as recent surgery, organ transplantation, valvulopathy, diabetes mellitus, AIDS, or cancer. Frequently, these conditions involve immunosuppressive therapy or antibiotic treatment, which may contribute to the development or selection of microorganisms (Zé Zé *et al.,* 2004).

While *Lactobacillus* species are generally considered non-pathogenic in the oral cavity, gut, and female genital tract, a case reported by Henry and Moss (2009) highlighted the potential for *L. acidophilus* to cause infective endocarditis. The patient, a 63-year-old woman with a history of ovarian cancer and multiple chemotherapy cycles, presented with symptoms of persistent cough, shortness of breath, and high fever. After receiving the initial antibiotic treatment, her condition worsened, leading to the need for transfer to the intensive care unit. A transthoracic echocardiogram showed a 2.4 cm circular echo-density formation on the atrial surface of the mitral valve, and blood cultures confirmed the presence of *L. acidophilus* infection. Consequently, the antibiotic regimen was modified to include ampicillin and vancomycin leading to the successful eradication of the infection and hospital discharge. The authors emphasize the diagnostic challenges associated with *Lactobacillus endocarditis* due to its nonspecific clinical presentation, which can delay appropriate treatment. However, early recognition and effective antibiotic therapy can be lifesaving.

According to a study by Asahara et al. (2003), instances of local or systemic infections, including septicemia, meningitis, and endocarditis, have been linked to lactic acid bacteria (LAB). Although the majority of LAB strains associated with clinical cases are attributed to *Enterococcus faecium* and *E. faecalis*, a few cases have been associated with *L. rhamnosus*, *L. casei* or *L. paracasei*, and *L. plantarum*. Endocarditis, an infectious inflammation of the endocardium, is a relatively frequent infection associated with lactobacilli, with certain species like *L. casei* and *L. rhamnosus* being more commonly linked to infective endocarditis. However, it's important to note that the overall rate of *Lactobacillus endocarditis* is very low. Among lactobacilli, *L. rhamnosus* strains have been most often isolated in cases of human sepsis (Table 2), leading to the suggestion that this specific *Lactobacillus* species may have a higher potential for translocation and pathogenicity compared to other species. Under conditions of extensive mucosal injury, *L. rhamnosus* has been observed to worsen intestinal inflammation and translocate to various extraintestinal organs (Daniel *et al.,* 2006).

Several studies over the past two decades have suggested that certain *L. rhamnosus* strains can exhibit pathogenic effects. Strains confined from endocarditis patients have illustrated hindering characteristics, such as platelet accumulation and official to fibronectin, fibrinogen, and collagen. In an assessment of platelet-aggregating activity by Walter and Ley (2011), all *L. rhamnosus* strains isolated from infective endocarditis cases exhibited positive aggregation, possibly linked to proteins associated with the intestinal epithelium. The exact mechanism underlying this phenomenon remains unclear, but one suggestion is that these characteristics could enhance the organism's survival and colonization of vascular

surfaces. Moreover, both *L. rhamnosus* and *L. paracasei* subsp. paracasei exhibit the capacity to generate enzymes that assist in the decomposition of glycoproteins and fibrin clots found in humans (Simkins *et al.,* 2013), leading to speculation that these properties might contribute to infective endocarditis development. Nevertheless, the validity of this theory has sparked disagreement, as various types of Lactobacillus and Bifidobacterium have been proven incapable of breaking down intestinal mucosal glycoproteins through enzymes (Westermann *et al.,* 2016). Considering the crucial importance of probiotic attachment to the intestinal lining for successful colonization, it is imperative to conduct further investigations on their enzymatic functions on human intestinal cells.

A few documented cases have linked probiotic strains ingested orally with those found in clinical samples. For instance, Land et al. (2005) described a pediatric case where a Lactobacillus strain, identical to the *L. rhamnosus* GG strain given to a six-week-old infant undergoing heart surgery, caused invasive disease. The infant, who initially had non-bloody diarrhea, received a daily dose of one Lactobacillus GG capsule (containing 10×10^9 cells per capsule) through a gastrostomy tube for its probiotic benefits. Although the diarrhea improved, the infant later developed new-onset fever and significant leukocytosis. Blood cultures showed the presence of over 100 cfu of gram-positive rods/ml, identified as *Lactobacillus* species, and DNA fingerprinting analysis confirmed that they were indistinguishable from the probiotic strain. Discontinuing oral *Lactobacillus* GG therapy led to clinical improvement, suggesting a potential link between invasive disease and probiotic lactobacilli. Notably, preliminary findings from in vitro studies (Cabana *et al.,* 2006) and animal models suggest potential benefits of using inactivated probiotic preparations, making them a preferable option for children at an increased risk of bacteremia due to probiotic therapy (Liong and Shah, 2005).

In a recent study by Antoun et al. (2020), a case of endocarditis in an adult was reported. The patient had been taking a probiotic supplement containing *L. rhamnosus*, and interestingly, the strain found in the patient's blood cultures matched one of the strains found in the probiotic capsules. These strains showed similarities in various tests, including culture appearance, antimicrobial susceptibility patterns, and pyrolysis mass spectrometry results. Furthermore, there have been a few cases where Lactobacilli, including *Lactobacillus acidophilus*, were found to be associated with liver abscesses. Naqvi et al. (2018) documented the first case of a liver abscess caused by a *Lactobacillus rhamnosus* strain that was identical to the *L. rhamnosus* strain GG in a 74-year-old woman with a medical history of hypertension and non-insulin-dependent diabetes mellitus.

2.10 Antibiotic resistance in translocations and infecting strains

Crouzet et al. (2018) conducted an extensive study spanning 53 years and more than 200 cases to explore the impact of probiotic infections. Their findings revealed that when it came to treating probiotic infections, particularly those involving *Lactobacillus* spp., antibiotics such as penicillin or cephalosporin were commonly prescribed. In some cases, a combination of these antibiotics and an aminoglycoside was used to achieve synergistic effects. In vitro sensitivity data showed that this antibiotic therapy was effective in treating infections in 74% of cases. However, the study also noticed a decrease in sensitivity to antibiotics like vancomycin, cefazolin, and ciprofloxacin in patients with Lactobacillus bacteremia, with less than 50% of isolates showing sensitivity. Another study by Das et al. (2020) similarly found high levels of vancomycin resistance in lactobacilli.

To eradicate Lactobacillus infections that are resistant to antibiotics, it may be necessary to administer larger doses of antibiotics or use a combination of different antibiotics. This could result in longer treatment periods and higher expenses. Furthermore, these strains can spread and cause infections in other vulnerable areas of the body, making management and patient outcomes more challenging. Additionally,

antibiotic-resistant genes can be found on transferable genetic components, making it easier for them to be transferred to other harmful microorganisms. This increases the risk of developing infections that are resistant to multiple drugs.

2.11 Lactobacillus sepsis associated with probiotic therapy in infants

Nosocomial infections and the risk of Necrotising enterocolitis (NEC) pose significant threats to the health and survival of preterm infants, necessitating effective preventive measures (Zhou *et al.,* 2023). Extensive research has explored the potential of probiotic supplementation as an intervention to mitigate the risks associated with NEC and nosocomial infections. Probiotics play a crucial role in enhancing the composition of enteric microbiota, counteracting the loss of beneficial gut commensals such as *Bifidobacterium* and *Lactobacillus* species. Preterm infants, often subjected to prolonged antibiotic regimens, delayed initiation of enteral feeding, and lacking access to human milk, are particularly susceptible to disruptions in their gut microbiota. These disruptions can facilitate the proliferation of pathogenic microflora and aberrant gut colonization. Probiotics, by acting to prevent the translocation of pathogens from the gut, have the potential to reduce the risk of NEC (Manzoni *et al.,* 2013).

Despite the widespread daily supplementation of probiotics to thousands of extremely and very preterm infants based on these considerations, there have been documented cases of sepsis attributed to Lactobacillus species in patients receiving probiotics. These cases include two preterm infants with short-gut syndrome (Kunz *et al.,* 2004), one child with short-gut syndrome, one infant with congenital heart disease, one child with cerebral palsy, and one preterm infant with intrauterine growth restriction (Land *et al.,* 2005). These reports align with previous concerns about the potential risk of infections due to Lactobacillus species, as documented in adult populations (Sadowska-Krawczenko *et al.,* 2014).

Lactobacillus species have been implicated in systemic infections in both probiotic-supplemented and non-supplemented infants and children (Thompson *et al.,* 2001). Both groups shared common risk factors, including immune deficiencies associated with prematurity, prior gastrointestinal or cardiac surgery, previous antibiotic treatment (particularly vancomycin), a history of necrotizing enterocolitis (NEC), ileostomy, malabsorption issues, and the presence of central venous catheters (CVC). While *L. rhamnosus* GG is generally considered a harmless component of the human gut microbiome, it has been linked to Life-threatening complications: sepsis, pneumonia, and meningitis in vulnerable neonates and children, especially in cases involving probiotic supplementation (Ohishi *et al.,* 2010).

These concerns regarding *L. rhamnosus* GG may also extend to other commonly used probiotics in preterm infants, such as Bifidobacterium species, as a few cases of bacteremia/sepsis have been documented in newborns. It is crucial to note that the incidence of severe infections associated with probiotics remains relatively low in comparison to the widespread use of supplementation for NEC prevention in thousands of preterm infants (Zbinden *et al.,* 2015).

While the precise mechanisms underlying Lactobacillus infection pathogenesis remain unclear, adhesion to the intestinal mucosa and subsequent colonization are widely recognized as critical steps in the process, contributing to prolonged persistence within the intestine (Agostoni *et al.,* 2010). This observation supports the hypothesis that prolonged daily probiotic supplementation, as seen in this and previous cases (AlFaleh and Anabrees, 2014), may pose a significant risk factor for the development of associated infections.

CONCLUSION

Recent advancements in in vitro modeling, gut microbiome sampling techniques, and reliable

identification tools have significantly improved our understanding of probiotic pharmacokinetics. Variations in strain behavior, including survival rates in different segments of Probiotic strain behavior in the gut and in vitro adhesion have been observed. While the issue of colonization remains to be definitively resolved, a limited study has suggested its possibility with certain strains. Further investigations are warranted to establish in vivo adhesion to the epithelium, potential colonization, and the influence of the delivery vehicle on probiotic efficacy. Dose-response studies are of paramount importance in this regard. These efforts, crucial for ensuring safety, seek to either confirm or challenge hypotheses such as the significance of a probiotic's human origin, its capacity for high survival, and its ability to adhere to the intestinal epithelium. Importantly, these efforts should address key questions regarding the optimal dosage, frequency, duration, and concentrations of probiotics in commercial preparations.

RECOMMENDATIONS

The proliferation of probiotic products marketed as functional foods and nutraceuticals has sparked regulatory concerns regarding their composition. As the probiotics industry expands, existing regulatory frameworks may need to be adapted to ensure global safety and meet consumer expectations. Further research is essential to address fundamental questions surrounding probiotic therapy, including its mechanisms of action, optimal dosage and treatment durations, strain origins and sources, strain-specific effects, and the validity of health-related claims.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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