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Probiotics and its Application in Humans: An Overview

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Probiotics are live microorganisms that have been identified as natural alternatives to antibiotics, which are typically used to treat bacterial infections causing many diseases in both humans and animals. It discusses the benefits and drawbacks of probiotics and presents evidence from recent clinical trials and experimental models, showcasing their potential to protect human and animal health. Probiotics have demonstrated potential in enhancing health and aiding in the treatment and prevention of various conditions such as antibiotic-associated diarrhea (AAD), irritable bowel syndrome (IBS), and periodontal diseases. The human gut harbors a diverse microbial community crucial for intestinal health. Disruptions in this microbiome are linked to diseases like inflammatory bowel disease (IBD), cancer, cardiovascular disease, and metabolic disorders. Probiotics help

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restore gut microbiota balance, particularly during antibiotic treatments, reducing AAD incidence. They alleviate IBS symptoms and maintain oral health by modulating oral biofilm, reducing pathogen colonization, and enhancing immune response. Additionally, probiotics exhibit anti-carcinogenic properties by inhibiting bacterial enzymes involved in carcinogen formation and binding aflatoxins, thereby reducing cancer risk. Although antibiotics are life-saving drugs for bacterial illnesses, their excessive and inappropriate usage has led to increased bacterial antimicrobial resistance (AMR) and host microbiota imbalance, or dysbiosis. AMR is a major global health threat, potentially leading to millions of deaths annually. Thus, finding and creating antibiotic substitutes is imperative. Evidence suggests that probiotics can counteract infections, modulate immune responses, and regulate gut flora to preserve overall human health. This analysis also examines the potential use of probiotics by their various mechanism to act against infections

Keywords: Antimicrobial resistance (AMR); alternative to antibiotics; probiotics; human health; IBS; oral health.

1. INTRODUCTION

1.1 Probiotics

Probiotics are “live microorganisms, which administrated in adequate amount, confer health benefits to the host” [1]. Most of the probiotic microorganisms belong to the bacteria, but it includes some yeast’s which are naturally found in some foods, may be added in some food products and also available as food supplements. Alternatively, probiotics can also be defined as “live microbial food supplements” that has beneficial effects on host by enhancing the microbial flora of the intestine [2].

“Probiotics should not be confused with prebiotics, were prebiotics are some complex carbohydrates such as Fructo-oligosaccharides and inulin, which act as a metabolic fuel for the probiotic microorganisms present in the gastrointestinal tract. [3,4-7]. “Mostly the probiotics are identified by their specific strain that includes Genus, Species and subspecies. They also contain an alphanumeric designation” [8].

The most important characteristics of probiotics is, it should be survive in the site where its beneficiary activity has been required. For a maximum effect, the strain should have a higher proliferation rate, should colonize in the specific location and should survive the host’s immune system. Most importantly the probiotic microorganism should not be pathogenic, allergic, mutagenic or carcinogenic (i.e.) the probiotic microorganism should not cause any adverse effects to the host [9,10].

“Among the vast bacterial genera, the most commonly used probiotic organisms are from the *genus Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, Bacillus* and *Streptococcus* and some yeasts belong to the *Saccharomyces sp”* [11,12]. “Among these vast bacterial genera of probiotics *Lactobacillus rhamnoses* GG was the first probiotic microbial strain that received most clinical attention” [13].

“Probiotics are being advertised in health food stores, supermarkets, and the media for a variety of uses. They are also becoming more widely available in the form of capsules, powders, and fermented milk beverages. This commensal intestinal microbiome plays a crucial role in bolstering the host's resistance against infections through various mechanisms. Moreover, the intestinal microbiota plays a vital role in nutrient synthesis and metabolism, contributing to the host's overall health and well-being” [14].

“Probiotics are beneficial against a broad range of pathological disorders, including diarrhea, constipation, polycystic ovarian syndrome, ulcerative colitis, anxiety and stress, inflammatory bowel disease, diabetes, and breast cancer, according to clinical research” [15]. “Through the synthesis of bioactive metabolites such hydrogen peroxide, organic acids, antioxidants, and bacteriocins, probiotics have been shown to impede the proliferation of gut microorganisms” [16].

This review aims to provide a comprehensive overview of antibiotic resistance and alternatives, focusing particularly on the role of probiotics and microbiota. We will investigate the mechanisms that underlie antibiotic resistance, consider w probiotics may help restore microbial balance, and look at how human immunity is influenced by the microbiota in order to fight infections. We will also assess the clinical data that suggests.

Table 1. Criteria for an ideal probiotic microorganism

S.no	Ideal probiotic characteristics
1	They should have high cell viability, and must be resistant to low pH and bile salt
2	It should possess the ability to persist in the intestine even if the probiotic strain cannot colonize the gut
3	They must be adhesive to the guts epithelium to cancel the flushing effects of peristalsis
4	They should be able to interact or to send signals to the immune cells associated with the gut
5	It should be of human origin
6	It should be nonpathogenic to the host
7	It should have resistance to processing
8	Must have the capacity to influence local metabolic activity

probiotics can be used in place of traditional antibiotics, and we'll talk about the difficulties and potential future developments in this quickly developing subject.

2. IDEAL PROBIOTIC PROPERTIES

To be an ideal probiotic microorganism, either the bacteria or yeast should possess certain characteristics or properties which are listed in table [17,18].

3. MECHANISM OF ACTION OF PROBIOTICS

"Several mechanism had been postulated regarding the mechanism of probiotics. Partial digestion of lactose and intestinal mucosal lactase activity stimulation has been postulated as a possible action occurred against some types of diarrheas. Lactobacillus used in fermented dairy products have active beta galactosidase to lower the lactose level in the dairy products, which may affect or reduce the severity of osmotic diarrhea due to rotavirus" [19].

"Probiotic microorganism usually shows their effects in the gastrointestinal tract and influence the intestinal microbiota" [20]. "Probiotics also exert the halt effect by nonspecific specific-specific and strain specific mechanism" [1]. The nonspecific mechanisms vary widely among strains, species, or even genera of commonly used probiotic supplements. These mechanisms include inhibition of the growth of pathogenic microorganisms in the gastrointestinal tract (by fostering colonization resistance, improving intestinal transit, or helping normalize a perturbed microbiota), production of bioactive metabolites (e.g., short-chain fatty acids), and reduction of luminal pH in the colon.

Species-specific mechanisms can include vitamin synthesis, gut barrier reinforcement, bile salt metabolism, enzymatic activity, and toxin neutralization. Strain-specific mechanisms, which are rare and are used by only a few strains of a given species, include cytokine production, immunomodulation, and effects on the endocrine and nervous systems. Through all of these mechanisms, probiotics might have wide-ranging impacts on human health and disease. Probiotic community also enhance the nutritive value by specific mechanism like secretion of several enzymes for the fermentation and non-digestible dietary residues and help in recovering lost energy in the form of short chain fatty acids.

4. PROBIOTICS AND HEALTH CONDI-TIONS

Numerous in vivo and ex vivo studies that have been published in the literature have demonstrated the potential use of probiotics as human antibiotic substitutes. For example, bacteria found in soil and lactic acid can reduce the number of pathogens like *S. aureus, L. monocytogenes, P. aeruginosa, and Candida albicans* that colonize human bodies by acting as bacteriostatic and bactericidal agents. Additionally, certain scientific trials have demonstrated their effectiveness in treating illnesses. But it's crucial to distinguish between the circumstances in which probiotics complement antibiotics and those in which they serve as stand-ins. Probiotics are helpful for replenishing the gut microbiota, but for many human health scenarios, antibiotics are still the first line of treatment for bacterial infections [21]. In certain conditions, such as periodontal disease, acne, recurrent Helicobacter pylori infections, and bacterial vaginosis, the use of probiotics may be an alternative to the clear or debatable use of antibiotics [22]. Lastly, there are

some circumstances where using antibiotics seems inappropriate and probiotics seem like a better choice, including in the case of acute diarrhea linked to Clostridium difficile [23].

Probiotics have shown a enhancement in the health, treatment and prevention of various conditions such as

- Antibiotic associated diarrhea caused by *Clostridium difficile*
- Irritable bowel syndrome
- Treatment of periodontal diseases etc.

4.1 Probiotics in Gut

"Human gut is composed of vast and diverse microbial communities associated with human intestinal health" [24]. "It is believed to be that, almost about 100 trillion microbial cells are present in the human gut and provide a broad range of metabolic functions to the host" [25]. "The large intestine contains strict anaerobic bacteria, which are categorized as either harmful or beneficial" [26]. "Moreover human intestinal microbiota are known to perform various functions in the host including intestinal development, homeostasis and protection against pathogenic bacteria" [27,28]. Failure in maintaining the gut microbiome leads to some negative changes in the host metabolism that are linked to various diseases such as irritable bowel disease (IBD), cancer, cardiovascular disease and some metabolic disorders.

4.1.1 Antibiotic Associated Diarrhea

It disturbs the intestinal microbiome and, by decreasing microbial diversity, can lead to a loss of microbial metabolism (resulting in osmotic diarrhea due to excessive fluid in the intestine), loss of colonization Antibiotics are another common cause of acute-onset diarrhea. Antibiotic treatment often resistance (resulting in increased numbers of infections by other pathogens), and increased intestinal motility. Up to 30% of patients who use antibiotics experience AAD.

Individuals receiving inpatient care are at significantly greater risk of developing AAD than individuals receiving outpatient care. Similarly, children younger than 2 years and seniors older than 65 years are at greater risk of developing AAD than other children and adults. Some antibiotics (e.g., erythromycin and penicillin) are associated with AAD more often than others [29,30].

Meta-analyses indicate that the use of any of a few species and strains (described below) of probiotics might reduce the risk of AAD by 51% [31]. However, the benefits of probiotic use to prevent AAD depend on the type of antibiotic that caused the AAD, the strain(s) of probiotic used, the life stage of the user (child, younger adult, or older adult), and whether the user is receiving inpatient or outpatient care. Positive associations between intakes of probiotics and reduced risk of AAD have been found in children and adults age 18 to 64 years but not in adults age 65 years and older [29].

Both LGG and *Saccharomyces boulardii* have been shown to reduce the risk of AAD. In a systematic review and meta-analysis of 12 RCTs with a total of 1,499 children and adults, treatment with LGG (4×10^8 to 12×10^{10} CFU) compared with placebo or no additional treatment for 10 days to 3 months reduced the risk of AAD in patients treated with antibiotics from 22.4% to 12.3% [30]. However, when the 445 children and 1,052 adults were evaluated separately, the difference was statistically significant in children only. Although the optimal dose of LGG is unclear, 1 to 2×10^{10} CFU/day reduced AAD risk in children by 71% [30]. Taking probiotics within 2 days of the first antibiotic dose is more effective than starting to take them later.

4.1.2 Irritable Bowel Syndrome (IBS)

It is a common functional disorder in the gastrointestinal tract, that is characterized by recurrent abdominal discomfort or pain, bloating and changes in stool form [32]. According to research patients with IBS have a pro-inflammatory bacterial species including Enterobacteriaceae which are abundant in patient and a corresponding reduction in the amount of *Lactobacillus sp* and *Bifidomacteriumsp* [8].

Several meta- analysis have assessed that the role of probiotics in patients with IBS have positive, modest and beneficial effects. Probiotics reduces the risk of IBS symptoms or maintain the symptoms below 21%.

4.2 Probiotics and Oral Health

It is well known that in the oral cavity a diverse population of microorganisms has been estimated to include more than 700-1000 bacterial species spread on the tongue, teeth and gums among these 20% are of streptococci

species. It is generally accepted that the oral health is affected by residing bacteria as well as individual age, health, nutritional status and lifestyle [33].

Research reveals that the conformation of positive activity of probiotic lactic acid bacteria in prevention and treatment of antibiotic associated diarrhea and many gastrointestinal diseases [34]. It is also known that probiotic bacteria including Lactobacilli and Bifidobacterium are good colonizers of gastrointestinal tract, vagina and oral cavity of humans [35].

The possible activities of probiotics in the oral cavity are

1. Antagonism with pathogens
2. Aggregation with oral bacteria
3. Interaction with oral epithelium

Through the process of 1 and 2, modulation of the oral bio-film composition will take place [36, 37,38,39]. It results in the reduced pathogenicity and carcinogenic potential of bio-film forming microorganism [36,40,41,42]. The final results will be clear path for caries, gingivitis and periodontal management [43,2,44,27,45].

Through the process of 3, the results point out the ability of probiotic bacteria to strengthen the epithelial barrier function [46,44,9,47]. In addition to this they also help in modulating the innate and adaptive immune response [48,49].

List 1. List of Strains and their effects

Strains	Effects
Lactobacillus reuteri	Reduction in salivary *Streptococcus mutants* [49]
Bifidobacterium DN-173010	Reduction in salivary *Streptococcus mutants* [50]
Lactobacillus brevis	Anti-inflammatory effect [51]
Streptococcus saivarius	Inhibition of black pigmented salivary bacteria [35]
Lactobacillus reuteri	Reduction in dental plaque and gingitivitis [52]

4.2.1 Halitosis and probiotics

Halitosis or bad breath is primarily caused by the anaerobic bacteria responsible for periodontal disease [53]. Some of the halitosis causing oral bacteria include *Prophyromonasgingivalis, Treponema denticola, Treponema forsythia* [54, 55,56]. Halitosis is caused by the volatile sulfur compounds due to the degradation of sulfur containing amino acids. This problem could be rectified by reduction in the halitosis causing bacteria or its replacement by colonization of probiotic strains would elevate the treatment, management and control of halitosis [29].

4.3 Anti-carcinogenic Activity of Probiotics

Introduction of *Lactobacillus acidophilus* in the diet, lowers the formation of chemically induced colon tumor in rats [57]. A possible mechanism of these anticancer effects relies on the inhibiting the intestinal bacterial enzymes that converts the pro-carcinogens to the more proximal carcinogens [58]. Addition of Bifidobacterium longum to the diet of rats has shown to exert a strong anti-tumor activity on colonic mucosa [59].

Consumption of food with aflatoxin [AFB] contamination cause liver cancer. Some probiotic strains have been successfully shown to bind and neutralize AFB, in vivo and reduce the bio-absorption of AFB in the gut [60,58]. Normal intestinal flora can influence carcinogens by the production of enzymes like glucosidase, beta glucoroxidase, azo reductase and nitro reductase that converts procarcinogens to active carcinogens. Were Lactobacillus acidophilus and *Lactobacillus casei* supplementation helps in decrease in the levels of these enzymes [61,62].

4.4 Effects of Probiotics in People with Weakened Immunity

Immunomodulatory function is one of the notable activities of the probiotics. These functions demonstrated the interactive with immune cells such as monocytes, lymphocytes, macrophages and dendric cells. Some probiotics that are orally administered such as *Lactobacillus casei, L. acidophilus. L. rhamnosus, Lactobacillus delbrueckii subsp. Bulgaricus* and *L. lactis* had shown an increased number of intestinal IgAs. Probiotics also stimulate the clonal expansion of B cell that induce the release of IgAs without disturbing CD4 + T cell count [63].

Orally administrated probiotics are capable of improving the immunity in old age peoples [64]. Enhanced immune systed has been observed and reported during the administration of live *Bifidobactrium lactis* HN019 into their diets [65].

In some animal and human trails, probiotic have some beneficial effect in the prevention and treatment of some wide systemic condition. It includes inflammatory and autoimmune disease. Some strains have demonstrated stimulation of the immune response, thereby beneficial to immunodeficiency patients [66].

Systemic Lupus erythematous (SLE). A autoimmune disease involving wide organ such as skin, joints, kidneys and CNS. It is characterized by the formation of large number of antibodies against doble stranded DNA and also characterize by immune intolerance and self antigens [67].

In this study, several strains of probiotics such as *Bifidobacterium bifidi* and *Lactobacillus casei* strains shows significant reduction in the inflammation and restore tolerance in SLE animal models [68].

4.5 Effects of Probiotics in Gut Lines

It is essential to maintain the homeostatic relationship with the microbiota has been essential factor in the human immune system evolution and for the host metabolism and function [69].

The gastrointestinal mucosal Barrier prevents the diffusion potential injurious factors from the gastrointestinal lumen to the systemic circulation [70]. Disruption of the gut mucosal, barrier result in the permeability to allergens toxin and pathogen leading the immunological stress and inflammation [71,72].

Lactobacillus sp have been administered to subject that shown to be protective against pathogen infection and successful to treat diarrhoea in clinical trails [73].

L. plantarum administration helps in reducing the permeability of methotrexate induced colitis in intestine [74]. L. Case DN- 11400 lysates prevent the intestinal inflammation due to dextran sodium sulfate by improving the gut barrier function [75]. *Lactobacillus sp* also interacts with the various immune the epithelial cell function [76].

These are several mechanism associates with the mucosal layer protection by probiotic. Various strains of *Lactobacillus sp* and *Bifidobacterium sp* compete with the pathogen in the intestine to bind with the intestinal epithelial cells and displace pathogen from the host. It also interferes the adhesion of gastrointestinal pathogen through steric hindrance and competitive exclusion. By this probiotic maintain the cellular cytoskeleton and gut barrier integrity [77]. These also presents the adhesion of the pathogen on the intestinal mucosal layer by secreting lectin like bacteriocins [78].

5. ANTIBIOTICS AND AMR

Antimicrobial agent is natural or artificially synthesized substance that can inhibit or kill the growth of pathogenic organism. By discovery of antimicrobial agent has been saved millions of people life by kills pathogenic organism which cause the serious infection to them [79]. The overuse and misuse of antibiotics have accelerated the development of resistance mechanisms in pathogens, rendering many antibiotics ineffective. In 1928, penicillin was first made available [80]. Following that, penicillin-resistant bacteria emerged in the 1940s, making news [81]. Later, a number of antibiotics were introduced to the market to combat this resistance. Antibiotic resistance is a crisis that the world is currently experiencing.

Antimicrobial resistance (AMR) is a global problem for which several causes are suspected, including poor hygiene, misuse, and overuse of antibiotics. Antimicrobial resistance poses significant threat to global health, necessitating the exploration of alternative strategies. The main obstacles include rising rates of illness and mortality, rising medical expenses, and the protracted nature of infectious diseases. Since AMR results from genetic changes, resistant bacterial isolates can be found anywhere in the world, particularly in a range of sources such as soil, water, plants, animals, and humans. Recent data suggest that antibiotic resistance is an ongoing issue that has persisted from the past to the present. The UK government predicts that morbidity and mortality will reach 10 million by 2050 [82]. This indicates that deadly bacterial diseases spread quickly in the absence of effective control.

5.1 Basic Concept of Antibiotics

The word "antibiosis," which denotes the antagonistic effects of bacteria, is where the etymology of the word "antibiotic" originates [83]. While the term "antibiotics" refers to naturally occurring compounds that either kill or inhibit bacteria, the term "antimicrobials" was coined to describe naturally occurring, semi-synthetic, and

synthetic substances that have the ability to prevent the growth of bacteria, viruses, fungi, and parasites [84].

Antibiotics can be categorized based on their sources, administration routes, activity spectrums, action modes, and molecular structures [84]. *Streptomyces* spp., filamentous *Actinomycetes*, are the primary producers of antibiotics. Antibiotic compounds are also produced by fungus (*Penicillium*) and other bacteria (*Bacillus* and *Pseudomonas*) [85].

In the context of human health, antibiotics are currently used to treat infections and prevent the growth of pathogenic bacteria. The primary modes of action of antibiotics include inhibition of cell wall formation, disruption of cell membrane structure or function, inhibition of nucleic acid structure and function, inhibition of protein synthesis, and blocking of the major metabolic route that leads to the creation of folate [86].

5.2 Antimicrobial Resistance (AMR) Issues

Prominent organizations like the US Centre's for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and the World Health Organization (WHO) [87,88] have taken notice of AMR due to the rising abuse and misuse of antimicrobial agents in recent decades. "The ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial agent (like antibiotics, antivirals, and antimalarial) from working against it" is the definition of antimicrobial resistance (AMR). Standard therapies become ineffective as a result, and infections continue and may spread to other people. AMR increases the severity, incidence, and cost of an infection due to the decreased efficacy of antibiotic therapy. It is also linked to resistance against harmful pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus, Enterobacteriaceae*, and *Escherichia coli* [89].

The Centre's for Disease Control and Prevention (CDC) estimates that antibiotic resistance causes roughly 2 million illnesses and 23000 deaths annually in the United States. At the same time, AMR-related causes of death for human patients account for 25,000 fatalities annually in Europe [17].

The enhanced spread of AMR is caused by mutations or by the acquisition of mobile genetic elements containing resistance genes. Transduction, conjugation, and transformation are the most likely processes by which AMR genes are transferred. During the conjugation and transduction processes, plasmids transfer genetic material and functional genes from a virus (coding the gene or delivery of non-viral DNA). When the cell can integrate the exogenous DNA into its genome, transformation takes place [90,91,92]. The presence of resistance genes in transposable elements, such as plasmids, reduction in the uptake of antimicrobial agents (efflux of the antibiotic from the cell, biofilm formation, and permeability reduction), the presence of factors that affect the target antibiotic, such as enzymes, and mutation or alteration in the antibiotic target site are the main AMR mechanisms developed by resistant pathogens.

5.3 Alternatives to Antibiotics

Considering the alarming consequences of AMR, new antibiotic alternatives that are more targeted while removing harmful side effects on the gut. These substitutes seek to minimize the unwarranted and excessive application of antibiotics and ought to yield the same advantageous outcomes of such potent compounds.

Among the alternative candidates include microbial-based substitute classes like bacteriophages and molecular substitute classes like bacteriocins, antimicrobial peptides, medicinal botanicals, and nanoparticles, which function directly by preventing or eliminating infections. some vaccinations as well as probiotics [93]. The latter's antibacterial processes rely on either direct or indirect actions. Bacteriophages, for example, are viruses that infect bacteria and release their genetic material, which breaks down the DNA ofthe bacteria and eventually kills them. Probiotics have the ability to reduce dysbiosis and bacterial infections by modulating the host's gut microbiota and immune system. Alternatively, probiotics can act directly through antibiosis by producing metabolites such as bacteriocins, organic acids, antioxidant compounds, and nutrient-space competition.

According to their roles, two alternative groups are identified: (i) disease prevention via immune system stimulation (e.g., vaccines) and gut

microbiota and modulation (e.g., probiotics); and (ii) disease treatment via suppression or reduction of bacterial infections (e.g., phage therapy, Bacteriocins, anti-virulence inhibitors that sense quorum, nanoparticles, and antibodies [93].

6. PROBIOTICS AS POTENTIAL ALTERNATIVE TO ANTIBIOTICS

One potentially useful tactic to stop the spread of microorganisms resistant to antibiotics is the probiotic-based approach. Live bacteria, which make up probiotics, are advantageous to the human when handled properly. Probiotics are live microorganisms (bacteria or yeast) that colonies the host and produce health benefits. Among the most well-known probiotics are lactic acid bacteria species, including Enterococcus, Lactobacillus, Streptococcus, and Lactococcus, as well as Bifidobacterium [94,95,96]. Due to their unique properties, these microorganisms can withstand harsh environments found in their host organism, including acidity and enzymatic action. Through biological roles and microbiome regulation, they can colonies the host and promote health [97]. Probiotics work primarily through the production of antimicrobial compounds, modification of the immune system, enhanced adhesion to the intestinal mucosa and inhibition of microbial adhesion, as well as the competitive exclusion of pathogenic microorganisms.

Probiotics may be utilized to cure and prevent infectious diseases in both human and animal health [98], according to available data. For example, numerous clinical studies show that *Saccharomyces boulardii*, a probiotic yeast, reduces the problems associated with Candida infections [99]. By using processes of competitive exclusion and cytokine release promotion, *Lacticaseibacilluscasei* ATTC334, *Bifidobacterium brèvi* JCM1192, and *Bifidobacterium infantis* BL2416 might reduce the detrimental effects and mortality in chicks caused by Salmonella infections [100].

The following lists the primary antimicrobial mechanisms that probiotics use: immune system regulation, mucin and tight junction protein expression, competitive exclusion, improved intestinal barrier function, and antimicrobial molecule generation [101].

In recent years, the role of probiotics and the microbiota in mitigating antimicrobial resistance has garnered increasing attention. Probiotics and microbiota offer promising avenues for combating antimicrobial resistance. Probiotics are living microorganisms that provide health benefits when ingested in adequate amounts [102]. Most probiotic bacteria are Gram-positive, and their main functions are related to modulation and maintenance of the intestinal tract health [103]. The intestines host a diverse community of probiotic microorganisms, making it the primary site for colonization. They are stable in bile and acid, can be administered orally, and are believed to stick to the target gastrointestinal epithelium.

Over the past three decades, research on the effects of live microorganisms known as probiotics on replacing the unbalanced normal microbiota has increased due to the growing body of evidence regarding the impact of gut microbiota on overall health [34]. Since 1971, scientists have worked to elucidate the data demonstrating the protective effects of probiotic intake on a range of illnesses [104]. Probiotics have been shown to aid with gastrointestinal (GI) ailments, infectious diseases, cardiovascular disease, and cancer-related issues [105].

6.1 Competitive Exclusion of Pathogens

In order to stop prospective infections from growing too quickly, a probiotic bacterial community that has established itself in the gastrointestinal system creates competition for resources or adhesion sites. There are two competing tactics: interference competition and exploitation competition. An indirect mechanism is the competition for nutrients and space through exploitation. It is caused by the production of extracellular molecules (such as proteases and iron-chelating siderophores) that can hydrolyze complex macromolecules, limiting rivals' access to resources and causing a rapid consumption of nutrients. Additionally, probiotics have the ability to quickly occupy vacant spaces and outcompete infections by producing receptors and adhesins that attach to particular surface characteristics [106].

Through the synthesis of antimicrobial substances like bacteriocins, which damage pathogens, interference competition directly affects potential pathogens. Additionally, it lessens superinfections caused by antibiotics and helps to restore the intended the body's microbial population. Salmonella enterica and pathogenic Escherichia coli are effectively displaceable and competitively displaced from

their adherence by probiotic strains of *Lactiplantibacillus plantarum* [107].

6.2 Improvement of Intestinal Barriers

An essential part of both health and illness is the intestinal barrier. It ensures the mechanical, chemical, immunological, and microbial barrier activities necessary to maintain intestinal homeostasis, making it a crucial line of defense. Dysregulation and structural damage to the mucosa can impair these processes [108]. Probiotic usage is one method that the mucosal barrier may be able to employ to outcompete pathogenic organisms. Intercellular junction complexes and intestinal epithelial cells (IECs) maintain the mechanical barrier.

By increasing the expression of genes and proteins involved in tight junction (TJ) signaling and controlling the death of intestinal epithelial cells, probiotics can repair the gut barrier. the expansion of IECs. For instance, Lactobacillus acidophilus induces a fast and strain-specific increase in the function of the intestinal epithelial TJ barrier, which is mediated by the heterodimeric complexes of Toll-like receptor-2 (TLR-2) and TLR-2/TLR-1 and TLR-2/TLR-6. This results in protection against intestinal inflammation [109].

Additionally, goblet cells in the intestinal epithelium secrete a mucus layer. The mucus, which is primarily made up of high-molecular-weight glycoproteins known as mucins, promotes microbial absorption, gives resident bacteria somewhere to cling to, and inhibits entry. Probiotics can also cause the goblet cells to express mucin and secrete mucus. The expression of MUC2 and CDX2 as well as the production of mucin proteins were increased when probiotic mix yoghurt supernatants (*Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Bifidobacterium bifidum* (C-Bb); *S. thermophilus, L. bulgaricus,* and *L. acidophilus* (C-La); and *S. thermophilus, L. bulggaricus,* and *Lactobacillus gasseri* (C-Lg)) were applied to mucus-secreting colon epithelial cells (HT29-MTX). A significant mucin protein in the mucus layer is MUC2, and CDX2 controls MUC2 expression [110].

6.3 Secretion of Antimicrobial Peptides (AMPs)

Probiotic bacteria have the ability to create and release antimicrobial chemicals that have selective activity against various types of germs usually present in the gut. Examples of these molecules are diacetyl, hydrogen peroxide, organic acid compounds, and peptides. The term "bacteriocins" is frequently used to describe AMPs, which are a diverse class of peptides synthesized ribosomaly. These peptides either eradicate or stop pathogen development within the lumen [111]. Generally speaking, bacteriocins fall into three classes: Heat-stable peptides of class I are antibiotics with linear (A-antibiotics) or globular (B-antibiotics) linear structures and characteristic polycyclic thioether amino acids (e.g., lanthionine, <5 KDa); 2. heat-stable peptides of class II are bacteriocins without lanthionine (<10 KDa); and 3. heat-labile high-molecular-weight molecules are class III bacteriocins (>30 KDa) [105]. Probiotic bacteriocins possess antimicrobial mechanisms that rely on their structure, such as net charge and amino acid sequence. These mechanisms also involve pore formation, enzyme activity regulation, and quorum sensing, which refers to the capacity to identify and react to cell density of population combined with gene regulation [112].

Because class I bacteriocins can penetrate the cell membrane, they are harmful to the integrity of the cell. Inhibition of cell wall production is one of class I bacteriocins' additional mechanisms of action. While those of class III directly lyse cells, those of class II can depolarize cell membranes by attaching to the membrane pore receptor system, such as mannose phosphotransferase [113]. For example, the AMP called nisin can interact with lipid II proteins that are attached to membranes to create pores in the cell membrane, which causes the bacteria to lyse [114]. These bacteriocins are members of the positive-charged A-antibiotic class and are generated by *Lactococcus lactis.*

Mersacidin, a globular-shaped, neutrally or negatively charged peptide found in Bacillus species, is a class I B-antibiotics that can obstruct the production of cell walls [115]. With regard to S. aureus (ATCC 25923), E. coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 25619), and Listeria monocytogenes (ATCC 15313), the class II bacteriocin known as pediocin from *Pediococcuspentosaceus* GS4 (MTCC 12683) exhibits antibacterial and antagonistic potential [116]. Class III bacteriocins include the AMPs colicin, megacin, klebicin, helveticin I, and enterolysin from Salmonella pneumonia, Lactobacillus helveticus, Enterococcus faecalis, and Bacillus megaterium, respectively. Cell wall hydrolysis is something they can catalyze [112].

6.4 Modulation of Host Immune System

Probiotic bacteria may boost the development of beneficial elements in the gut microbiome in order to produce their immunomodulatory effects. A probiotic can improve nutritional and environmental proto-cooperation, which helps the body control both specific and nonspecific immune responses, by reestablishing the natural ecological niche [117]. The first line of defense, known as innate immunity or the nonspecific immune response, is made up of immune cells such as dendritic cells, macrophages, monocytes, neutrophils, and natural killers, as well as cytokines, which are immunomodulatory agents. Skin and mucous membranes are examples of physical barriers. In response to offensive targets, lymphocytes (B and T cells) stimulate the particular immune response (adaptive immunity) through the creation of antibodies, the generation of immunoglobulins, and the cell-mediated immune response [118].

Probiotics affect innate immunity by increasing macrophage phagocytosis and natural killer (NK) cell cytotoxicity. By interacting with intestinal immune cells such enterocytes, dendritic cells, and regulatory T cells, they regulate adaptive immunity [119].

By restoring the immune system, the benefits of replenishing the gut population with probiotics extend beyond preserving a healthy gut habitat. Probiotics have a variety of effects on the host defense mechanisms, including phagocytic activity stimulation, pro- and anti-inflammatory cytokine balance, and increased cytokine and immunoglobulin IgA synthesis.

6.5 Stimulation of Phagocytic Activity

It is possible to strengthen nonspecific immune responses with probiotic bacteria. The stimulation of phagocytic activity by macrophage activation is one of the potential mechanisms. By encouraging the synthesis of cytotoxic chemicals like nitric oxide (NO) and secreting immunoregulatory cytokines like interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and interferon-η (IFN-γ) to start the pathogen destruction process, activated macrophages improve phagocytosis [120].The surface elements of probiotic LABs, such as proteins, flagella, capsular polysaccharides (CPSs), lipopolysaccharide (LPS), and peptidoglycan (PG), can bind to particular receptors on macrophages called pattern recognition receptors, or PRRs. These components represent microbial associated molecular patterns (MAMPs) [121].

It has been suggested that in healthy adult volunteers, consuming fermented milk containing *Lactobacillus johnsonii and S. thermophilus* increases the phagocytic activity of peripheral blood leukocytes [122]. In a different investigation, feeding peritoneal macrophages fermented fish protein concentrate (FPC) at 0.3 mg/mL for seven days in a row improved the phagocytic activity of the cells in a mouse model. This discovery suggests that via improving pathogen phagocytosis, fermented fish proteins control nonspecific host defense mechanisms.

6.6 Balancing of Pro- and Anti-Inflammatory Cytokines

Small proteins called cytokines are generated by immune cells, including natural killers, T cells, B cells, and macrophages, to control and affect the immune response [123]. Due to its involvement in the control of inflammation, cell activation, growth, and differentiation, cytokine production has the potential to modify the host immune system. Pro- and anti-inflammatory cytokines must be in balance for the inflammatory process to occur. Pro-inflammatory agents include interleukin-1 (IL-1), IL-2, IL-6, IL-12, IL-18, gamma interferon (IFN-γ), and tumor necrosis factor alpha (TNF-α). Pro-inflammatory cytokines, chemokines, and chemokine receptors are inhibited by anti-inflammatory cytokines like IL-10 and transforming growth factor-β (TGF-β) that are produced by monocytes, T cells, B cells, macrophages, natural killer cells, and dendritic cells.

Probiotics interact with intestinal enterocytes, dendritic cells, Th1, Th2, and Treg cells to induce the production of cytokines, which in turn regulates the innate and adaptive immune systems. By significantly reducing the secretion of pro-inflammatory IL-1β and IFN-γ and increasing the expression of anti-inflammatory IL-4, IL-5, and IL-10 cytokines, *Streptococcus thermophilus* ST285 has been shown to change pro-inflammatory secretion to anti-inflammatory secretion against multiple sclerosis peptide in mice Furthermore, *S. thermophilus* ST285 enhanced the production of anti-inflammatory cytokines (IL-4, IFN-γ, and TNF-α) by human monocytes [124]. Yoghurt, the most widely recognized cultured dairy product, has been modified with particular lactic acid bacterial

strains to increase the synthesis of cytokines, such as interferon γ (IFN-γ) by monocytes and human blood mononuclear cells [125].

6.7 Enhancing Immunoglobulin A (IgA) Production

The first line of defense against infection in the digestive tract is IgA, which is produced by the plasma cells. Secretory immunoglobulin A (SIgA) guards against pathogen adherence and intestinal barrier penetration. When SIgA comes into touch with bacteria that are present in the digestive system, it agglutinates the pathogens and the pathogenic material, breaking up adhesive complex substances and adhering to the surface of the bacteria with adhesive proteins [126]. Probiotics have the ability to strengthen host defense by increasing the synthesis of total IgA and particular antibodies that are resistant to infections. It has been shown that LABs cause dendritic cells to produce IL-6 and IL-10, which helps to increase the concentration of secretory IgA at mucosal locations in humans [127].

There has been evidence of the immune-stimulating properties of fermented milk kefir prepared with a range of bacteria, including *aceterobacteria, leuconostocs, lactobacilli*, and some potentially helpful yeast. It was observed that young rats' IgA antibody titers significantly increased after consuming kefir, both in senescent and young rats [128]. Additionally, it has been demonstrated that eating yoghurt can change the way that plasma cells produce IgA in a dose-dependent way [129]. Salivary IgA levels rose after six weeks of administration of viable (Lactarius subsp. salicinius AP-32, *B. animalis subsp. lactis* CP-9, and *Lactobacillus paracasei* ET-66) and heat-killed (*Lactariussubsp. salicinius* AP-32 and *L. paracasei* ET-66) probiotics in healthy adults. These probiotics also inhibited oral pathogens like *S. mutans, P. gingivalis, F. nucleatum subsp. polymorphum,* and *A. actinomycete mcomitans* [130].

7. ADVANTAGES AND DISADVANTAGES OF PROBIOTICS AS ANTIBIOTIC ALTERNATIVES

Probiotics are live microorganisms that can act directly by creating antimicrobial metabolites and fighting with other microbes for sites and resources, or indirectly by boosting host immune systems. In contrast, antibiotics are drugs that are actively utilized to fight diseases. Additionally, probiotics lessen antibiotic-induced dysbiosis and aid in the restoration of a healthy microbiota in the gut. Probiotics can make up for the negative effects of antibiotics in this case. Furthermore, unlike antibiotics, which are primarily meant to inhibit or kill bacteria, probiotics have a variety of activities that may include antiviral, antifungal, and antibacterial properties [101]. Their status gives them additional characteristics that set them apart. Probiotics are readily available and typically ingested as diet supplements or through fermented goods, whereas antibiotics are used as pharmaceuticals that require a prescription from a doctor. However, some strains of probiotics, including *S. boulardii*, are given as drugs because they have antidiarrheal properties. A short-acting, low-dose antibiotic that is successful in terms of dosage, effects, and length of therapy, an effective antibiotic can induce a pathogen's defense mechanisms and kill beneficial bacteria, which can lead to gradual antimicrobial resistance and an imbalance in the host microbiota. On the other hand, probiotics frequently have noticeable benefits after prolonged use without the negative effects of antibiotic therapy. In actuality, probiotics can maintain the equilibrium of the host's microbiota and regulate pathogenic targets by competitively excluding nutrients and space. One of the drawbacks of probiotics is that they are sensitive to harsh stressors (such as changes in temperature, acidity, wetness, etc.), which lowers their survival rate and, consequently, their ability to colonize the gut.

8. CONCLUSION

Overuse and inappropriate use of antibiotics have led to increased incidences of pathogen resistance and dysbiosis, posing serious risks to the health and welfare of people and animals. As live, multifunctional microorganisms with many more properties and functions than antibacterial chemicals, probiotics appear to be solid alternatives. Probiotics offer additional modes of action against infections, such as space exclusion and nutrient competition, in addition to creating numerous antimicrobial metabolites similar to drugs and immunomodulation activities. These multi-action mechanisms raise the possibility of using probiotics as antibiotic alternatives while reducing the risk of pathogen antimicrobial resistance (AMR). Furthermore, probiotics can be used as antimicrobials against viruses in addition to bacteria. Many studies and

clinical trials have demonstrated the effectiveness of probiotics in suppressing pathogens in both humans and animals. This data supports their potential uses in illness prevention, infection treatment, and enhancing immunological function, growth performance, and nutrient efficiency. Probiotics have higher specificity and shorter treatment times than antibiotics. However, despite these benefits, maintaining cell viability and optimizing dosage remain practical obstacles. Probiotics play a significant role in enhancing health, treatment, and prevention of various conditions by maintaining and restoring the balance of the gut microbiome. They are particularly effective in preventing antibiotic-associated diarrhea, reducing symptoms of irritable bowel syndrome, and improving oral health by antagonizing pathogens and modulating biofilm composition. Additionally, probiotics have shown potential anti-carcinogenic effects by inhibiting the activity of intestinal enzymes that convert pro-carcinogens to carcinogens. Overall, the beneficial effects of probiotics span across gastrointestinal and oral health, highlighting their importance in both preventive and therapeutic healthcare.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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