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Review Article

Mechanisms and Applications of Probiotic Bacteria in the Control of Bacterial Infections

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Abstract

This research aims to evaluate the capacity of specific microorganisms, namely *lactobacilli* and other lactic acid bacteria (LAB), to eradicate antibiotic-resistant pathogens and establish novel therapeutic strategies. The increasing failure of conventional antibiotics against resistant strains underscores the critical need for effective alternatives. *Lactobacilli* have emerged as a promising candidate, demonstrating the ability to reduce pathogen virulence through multiple mechanisms, including the production of bioactive substances, competition for resources, and coaggregation. Beyond their antimicrobial activity, prolonged administration of these probiotics induces beneficial modifications in the gastrointestinal microbiome. This review summarizes the supporting evidence for *lactobacilli's* efficacy in treating various pathological conditions, including digestive disorders like diarrhea, metabolic imbalances, and even broader applications in kidney and pancreatic health, cancer prevention, and immune modulation. With their proven safety profile and multifaceted mode of action, *Lactobacilli* represent a viable, safe, and cost-effective alternative for combating resistant infections and promoting overall health.

Keywords: *Probiotic Bacteria; Treatment of Pathogenic Bacteria; Aantibiotic-Resistant Bacteria; Saccharomyces*

Introduction

Bacterial infections remain one of the most critical challenges in medicine, a status likely to persist. A primary complicating factor is the endogenous nature of many infections, where causative pathogens originate from the body's own bacterial flora. This presents a fundamental paradox: the bacterial microbiota is essential for human health, yet it simultaneously serves as a reservoir for potential pathogens capable of causing a wide spectrum of infections [1]. The cornerstone of treatment, antibiotic therapy, is now facing an unprecedented threat. Despite the prolific development and introduction of antibacterial drugs over the past 80 years, the rise of multidrug-resistant bacteria jeopardizes their efficacy. The growing prevalence of resistance mechanisms, such as broad-spectrum beta-lactamases and carbapenemases, raises the alarming possibility of a new "post-antibiotic era". In this scenario, effective treatments for infections caused by multidrug-resistant bacteria may no longer be available, underscoring the severe and escalating nature of this crisis [2]. Owing to their beneficial properties, several strains from this group are classified as probiotics-live microorganisms that confer a health benefit when administered in adequate amounts. Furthermore, their inactivated cells and cell-free supernatants (CFS), which contain beneficial components, are considered postbiotics, defined as inanimate microbial preparations that also benefit the host [3]. These bacteria are native members of the human microbiota, where they play a crucial regulatory role in host defense. They protect against pathogen colonization and confer other benefits, including enhanced nutrient assimilation and the stimulation of host tissues. The prolonged consumption of these probiotics modifies the gastrointestinal flora, thereby boosting the immune system and reducing the adhesion of pathogens. The critical importance of effective bacterial management is underscored by clinical studies. Herkel., *et al.* reported a stark, statistically significant difference in mortality for ventilator-associated pneumonia: 27% in patients receiving adequate antibiotic therapy versus 45% in those given inadequate treatment, often due to pre-existing resistance to the initial antibiotics [4]. An equally alarming development is the discovery of multidrug-resistant (MDR) bacteria within the normal microbiota itself. For instance, Arnan., *et al*. found that the prevalence of ESBL-positive *Escherichia coli* strains in neutropenic patients increased from 14% at hospital admission to 29% during their stay, indicating colonization with resistant strains. A study at the University Hospital Olomouc, Czech Republic, revealed a 21% prevalence of ESBL- and AmpC-positive *Enterobacteriaceae* in the gut microbiota of hemato-oncology patients [5]. Critically, genetic analysis confirmed that in two patients with clinical infections, the multidrug-resistant bacteria isolated from the blood and urine were identical to those found in their gastrointestinal tracts, indicating that the patients' own gut flora was the source of the subsequent life-threatening infections. The ubiquity of this threat is further highlighted by the environmental presence of multidrug-resistant bacteria, as documented in other studies within this Special Issue. The urgency of antimicrobial resistance (AMR) is most acute in critical care, where effective antibacterial therapy must often be initiated within hours of diagnosis [6]. This narrow window frequently precludes the precise identification of the etiological agent and its antibiotic susceptibility profile, creating a significant therapeutic dilemma. Yet, the administration of adequate antibiotic therapy remains a cornerstone of positive patient outcomes. Addressing the multifactorial AMR crisis requires a concerted interdisciplinary approach. A key prerequisite is robust multidisciplinary collaboration and the implementation of comprehensive bacterial resistance surveillance. This surveillance must elucidate the selection pressures driving resistance and the pathways of its spread, including the underlying genetic mechanisms as explored in this issue. Such data are indispensable for formulating rational antibiotic policies and effective hygiene measures. Consequently, the practical implementation of antibiotic stewardship programs is essential. These programs are systematic measures designed to ensure rational antibiotic use through appropriate drug selection, optimal treatment duration, and correct administration routes [7]. A comprehensive strategy to combat antimicrobial resistance (AMR) must be multi-faceted, integrating strict hygiene protocols, the development of novel antibacterial agents, and robust public education on the growing threat of resistance. Central to this effort is the rational use of antibiotics. However, clinical practice often necessitates initial, non-targeted therapy for acute infections where diagnostic delays are risky. In these scenarios, the crucial factor is a sound clinical indication. Antibiotic use itself is a significant risk factor for selecting resistant strains, including those with intrinsic resistance (e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) and those with acquired resistance (e.g. MRSA, ESBL-producing Enterobacteriaceae). Therefore, antibiotic treatment must be reserved for clinically confirmed or highly probable bacterial infections, and prophylactic use "just in case" should be avoided as unwarranted and hazardous. When selecting an empirical regimen, clinicians must synthesize local epidemiological data with broader principles. This includes understanding bacterial pathogenesis, microbial properties, and antibiotic pharmacokinetics, alongside consulting national and international surveillance systems like EARS-Net [8]. Beyond managing resistance, alternative therapeutic strategies are emerging. Certain *lactobacilli*, for instance, exhibit antitoxic activity through their ability to neutralize microbial toxins and other harmful compounds, which is important for maintaining host health. This is particularly relevant given that conventional antibiotics can cause collateral damage to the host's beneficial microbiota. A classic example is antibiotic-associated diarrhea, which results from the disruption of these native microbial communities [9].

Common microbes used as probiotics

Probiotics encompass a diverse range of microorganisms, including bacteria, yeast, and molds. The most prevalent species used include:

- **Bacteria:**
  - Lactobacillus (e.g., *L. acidophilus, L. plantarum, L. casei, L. rhamnosus*)
  - Bifidobacterium (e.g., *B. bifidum, B. longum, B. breve, B. lactis*)
  - Other Genera: *Streptococcus thermophilus, Enterococcus faecium, Bacillus* spp., *Pediococcus* spp., *Leuconostoc mesenteroides*, and *Propionibacterium* spp.
- **Yeast and Molds:**
  - *Saccharomyces boulardii* (also spelled *bourlardii*)
  - *Saccharomyces cerevisiae*
  - *Aspergillus oryzae*
  - *Candida pintolopesii.*

The repertoire of probiotic strains continues to expand due to ongoing research and the discovery of novel microorganisms with beneficial properties. Staying informed of this evolving field is essential for understanding their full potential.

Probiotics for health improvement

A primary focus of probiotic research is their role in promoting and maintaining health in the general population. The underlying premise is that consistent use by healthy individuals can enhance overall well-being and build resilience against various illnesses [10]. This proactive approach represents a strategic form of preventative healthcare. The mechanisms through which probiotics confer these benefits, both direct and indirect, will be elaborated in the following sections.

Microbial balance: Beneficial vs. pathogenic microbes

The human body, particularly the digestive system, hosts a complex consortium of microbes that perform essential functions, including nutrient digestion and absorption. A balanced gut microbiota efficiently breaks down complex food structures and compensates for digestive deficiencies. Conversely, an overabundance of pathogenic ("bad") microbes can disrupt this harmony. These organisms may impair proper digestion and release toxins, leading to a cumulative negative impact on health with each exposure. Many chronic health issues are misdiagnosed, while their root cause is often a dysbiosis-an imbalance in the gut microbiota driven by poor diet, lifestyle, or illness. This state creates an environment where harmful microbes thrive at the expense of beneficial ones. In such cases of dysbiosis, therapeutic intervention with higher dosages of specific probiotics is often necessary to restore a healthy microbial equilibrium [11].

Probiotic mechanisms: Restoring microbial balance

Probiotics function primarily by counteracting harmful microbes and restoring a healthy balance to the gut microbiota. When pathogenic bacteria colonize the digestive system, they can ferment food improperly and produce toxins, adversely affecting health. Probiotics introduce beneficial microbes that compete with these pathogens, correct the fermentation process, and support overall well-being. The necessity for probiotic supplementation arises from various factors that deplete our native beneficial flora. These include exposure to environmental pathogens and, notably, the use of antibiotics, which non-specifically destroy both harmful and beneficial bacteria. Incorporating probiotics into the daily diet is an effective strategy to continuously replenish and maintain a healthy microbial community, a practice supported by historical dietary traditions [12]. In cases of severe dysbiosis, higher therapeutic doses in the form of tablets or concentrates may be necessary. A healthy gut is characterized by a balanced equilibrium of bacterial groups, including

Lactobacilli, Bifidobacteria, Streptococci, and *Bacteroides*. This balance is vulnerable to disruption by numerous exogenous and endogenous factors such as stress, poor diet (high in fat and sugar), medication, and environmental toxins. The beneficial microbiota is essential for health, playing a crucial and spontaneous role in training the immune system and performing metabolic functions, such as aiding lactose digestion, that the human body cannot accomplish alone [13]. Pathogenic bacteria can persist at low levels without immediate symptoms, but their negative effects may manifest over time or when their populations expand considerably. In a healthy state, beneficial microbes suppress these potential pathogens by occupying ecological niches and competing for resources, a phenomenon known as colonization resistance. However, modern lifestyle choices often disrupt this balance, favoring the growth of harmful bacteria. Probiotics represent the most natural solution to this imbalance, employing the principle of competitive exclusion. The beneficial bacteria in probiotics directly compete with pathogens for space and nutrients, thereby suppressing their growth and reducing them to minimal, harmless levels. The gastrointestinal tract, hosting an estimated 100 trillion microbes, has innate defenses against pathogens. The stomach's acidic environment serves as a primary barrier. However, some pathogens can produce ammonia, which locally alkalinizes the intestinal environment to enhance their survival. This is where certain probiotic foods, like fermented milk, offer a dual benefit: their mild acidity can help inhibit pathogens, while the live microbes they contain directly replenish the beneficial flora, promoting a sense of well-being and a restored microbial equilibrium. Furthermore, fermented milk provides additional benefits; it contains proteins that can buffer excess stomach acidity. *Lactobacillus*, a key strain naturally found in such products, is a prime example of a beneficial microbe [14].

The gastrointestinal microflora performs a suite of crucial functions that are essential for host health. These include:

- **Colonization resistance:** Occupying ecological niches to prevent pathogen establishment.
- **Digestive support:** Aiding in food breakdown and fermenting complex dietary fibers that are otherwise indigestible.
- **Pathogen inhibition:** Producing antimicrobial compounds, such as lactic acid, to suppress the growth of harmful bacteria.
- **Synthesis of nutrients:** Secreting essential vitamins (e.g. B vitamins) and amino acids.
- **Immune modulation:** Interacting with and stimulating the host›s immune system to maintain a state of readiness.

Health benefits and mechanisms of action

Probiotics are beneficial microorganisms that confer health advantages primarily by colonizing the digestive tract and competing with pathogenic microbes. They function through several key mechanisms: enhancing nutrient absorption by fermenting food into simpler metabolites, producing essential vitamins and enzymes, and modulating the host's immune response. The population of these beneficial microbes can be depleted by factors such as poor diet, alcohol consumption, aging, and, most notably, antibiotic treatments. Therefore, their regular dietary intake is recommended for maintenance, with higher, therapeutic doses indicated following events like antibiotic therapy to restore the gut microbiota [15].

The health benefits of probiotics can be summarized as follows:

- **Pathogen inhibition:** They directly antagonize harmful microbes by producing antimicrobial compounds (e.g. organic acids, bacteriocins) and by competing for adhesion sites and nutrients.
- **Enhanced digestion and metabolism:** Probiotics improve the efficiency of food breakdown, which can enhance nutrient extraction and reduce the metabolic burden on the host digestive system.
- **Barrier fortification:** They contribute to the integrity of the intestinal mucosal barrier, protecting host cells from harmful compounds and pathogens.
- **Enzymatic compensation:** Probiotics can complement human digestive deficiencies, such as lactase insufficiency, by providing exogenous enzymatic activity (e.g. lactase).

- **Immunomodulation:** They interact with immune cells in the gut-associated lymphoid tissue, promoting a balanced immune response. It is crucial to note that the benefits of probiotics are dose-dependent, and their use should be evidence-based to ensure optimal efficacy and safety [16].

Role in infection control and antimicrobial resistance

While the precise mechanisms of probiotics are an active area of research, their role in infection control is well-established through several actions: modulating gut pH, secreting antimicrobial substances, competing with pathogens for resources and adhesion sites, and stimulating immune defenses (See table 1). A significant advantage of probiotics is their proven safety profile and cost-effectiveness as a therapeutic adjunct. In the context of rising antimicrobial resistance (AMR), probiotics offer a promising alternative strategy. In 1994, the World Health Organization recognized them as a critical next-line defense when conventional antibiotics fail. This application, known as microbial interference therapy, utilizes probiotic strains to prevent or treat infections by directly interfering with the colonization and growth of multidrug-resistant pathogens, thereby reducing the reliance on traditional antibiotics [17].

Mechanisms of action: How probiotics inhibit pathogens

Probiotics employ several key strategies to combat pathogenic microbes and support gastrointestinal health:

- Competitive exclusion: Probiotics outcompete pathogens for limited resources, including physical binding sites on the intestinal epithelium and essential nutrients, thereby suppressing their colonization and growth**.**
- Production of antimicrobial compounds: Beneficial strains synthesize and release various antimicrobial substances, such as organic acids (e.g., lactic acid), bacteriocins, and hydrogen peroxide, which directly inhibit or kill susceptible pathogens.
- Enhancement of gut barrier function: Probiotics contribute to the maintenance and strengthening of the intestinal mucosal barrier. This effect helps prevent the translocation of harmful bacteria and their toxins from the gut lumen into the bloodstream, a process known as “leaky gut”.
- Immunomodulation: By interacting with gut-associated lymphoid tissue (GALT), probiotics can modulate the host’s immune response, enhancing the ability to recognize and clear pathogens while promoting a state of balanced inflammation.

Therapeutic application: Probiotics in the management of diarrhea

Diarrhea is a common condition frequently stemming from:

- Antibiotic use: Which disrupts the commensal gut microbiota, often leading to antibiotic-associated diarrhea (AAD).
- Infectious agents: Including viruses (e.g. rotavirus), bacteria (e.g. enterotoxigenic *E. coli*), and parasites.
- Underlying digestive disorders: Such as irritable bowel syndrome (IBS), Inflammatory Bowel Disease (IBD), and Small Intestinal Bacterial Overgrowth (SIBO).

Probiotics alleviate diarrhea through multiple mechanisms, primarily by restoring the gut’s microbial balance. Clinically, they have been shown to reduce the duration and severity of acute infectious diarrhea and are effective in preventing antibiotic-associated and traveler’s diarrhea.

Specific probiotic strains with robust clinical evidence for diarrhea management include:

- *Lactobacillus rhamnosus GG*: Particularly effective in reducing the risk and duration of antibiotic-associated and infectious diarrhea in children and adults.
- *Saccharomyces boulardii*: A beneficial yeast proven to help prevent traveler’s diarrhea and reduce recurrences of *Clostridioides difficile* infection.
- *Bifidobacterium lactis*: Supports overall gut health and immune function, contributing to a reduction in diarrheal episodes.

Mechanisms of action and health improvement

Despite significant advances in probiotic research, a comprehensive understanding of their precise mechanisms of action remains an area of active investigation. Current evidence indicates that probiotics confer health benefits through several interconnected mechanisms:

- Competitive exclusion: Probiotics compete with pathogenic microbes for essential nutrients and adhesion sites on the intestinal epithelium, thereby inhibiting their colonization and survival in the gut.
- Production of antimicrobial substances: They function as natural antimicrobial agents by secreting compounds such as short-chain fatty acids (SCFAs), organic acids, hydrogen peroxide, and bacteriocins [18], which directly suppress the growth of harmful bacteria.
- Enhancement of intestinal barrier function: Probiotics strengthen the gut barrier by stimulating the production of mucins and modulating the expression of tight junction proteins (e.g. occludin, claudin-1), thereby reducing intestinal permeability and preventing the translocation of pathogens and toxins.
- Immunomodulation: They interact with the gut-associated lymphoid tissue to regulate local and systemic immune responses, promoting a balanced state of defense against pathogens.
- Neurological and metabolic interactions: Emerging research suggests certain strains can produce neurotransmitters and other bioactive molecules, indicating a role in the gut-brain axis and metabolic health. These multifaceted mechanisms underpin the role of probiotics not only in managing disease but also in promoting overall health and preventing various illnesses. By maintaining a balanced gut microbiota and supporting core physiological functions, probiotics represent a proactive strategy for enhancing general well-being and building resilience against a spectrum of health disorders [19].

Probiotic mechanisms: Restoring microbial balance for health

The gastrointestinal tract is a complex ecosystem where microbial balance is paramount. Colonization by pathogenic microbes can lead to improper fermentation of food and the production of toxins, adversely affecting host health. Probiotics counter this by introducing beneficial microorganisms that neutralize harmful ones, correct fermentation processes, and support overall well-being. The necessity for probiotic supplementation arises from frequent disruptions to the native gut microbiota. Exposure to environmental pathogens, lifestyle factors, and particularly antibiotic treatments can severely deplete beneficial bacterial populations [20]. Incorporating probiotics into the daily diet is an effective strategy for ongoing maintenance of gut flora, a practice with historical precedent in many traditional cultures. In cases of severe dysbiosis, higher therapeutic doses in pharmaceutical forms are indicated to rapidly restore microbial equilibrium. A healthy gut is defined by a balanced consortium of microorganisms, including genera like *Lactobacillus*, *Bifidobacterium*, and *Bacteroides*. This balance is vulnerable to disruption from a wide array of factors, including diet, stress, medications, and environmental toxins. The beneficial microbiota is not passive; it performs essential functions for the host, such as aiding in the digestion of complex fibers and lactose, synthesizing vitamins (e.g., B vitamins) and amino acids, and training the immune system for effective pathogen response. A key mechanism of protection is colonization resistance, where commensal bacteria occupy ecological niches and compete for nutrients, thereby suppressing the growth of potential pathogens. Pathogens often exist at low, subclinical levels but can cause significant harm when their populations expand, sometimes by altering the local gut environment to favor their own survival (e.g., by producing ammonia to increase pH). Modern lifestyles often shift the balance in favor of harmful bacteria, leading to a state of dysbiosis and health deterioration. Probiotics directly address this by leveraging competitive exclusion. A prime example is fermented milk: its mild acidity can help suppress pathogens, while the live microbes it contains, such as *Lactobacillus*, directly replenish the beneficial flora, supporting a robust gut environment and promoting overall health [21].

Infection control and clinical potential

While the precise mechanisms of action for probiotics continue to be an active area of research, their role in infection control is supported by several well-defined strategies. These include modifying the gut pH, producing direct antimicrobial compounds, competing with pathogens for binding sites and nutrients, stimulating immunomodulatory cells, and secreting digestive enzymes like lactase (See table 1). A significant advantage of probiotics is their established safety profile, cost-effectiveness, and demonstrated ability to interfere with microbial infections. In light of the global antimicrobial resistance (AMR) crisis, the World Health Organization recognized probiotics as a critical next-line defense strategy when conventional antibiotics lose their efficacy. This therapeutic approach, known as microbial interference therapy, utilizes beneficial microbes to prevent or treat infections by directly competing with and suppressing pathogenic agents, thereby offering a promising alternative to traditional antibiotics [22].

Pathogen	Gene(s)	Protein / System	Function in Virulence	Reference
Salmonella spp.	*avrA*	AvrA	Inhibits host innate immune responses	[23]
	hilA	HilA	Master regulator of *Salmonella* Pathogenicity Island 1 (SPI-1)	[23]
	hilC hilD	HilC, HilD	Promotes survival and replication within the host	[24]
	spv		Critical for intimate attachment to host cells (A/E lesions)	[25]
Escherichia coli	*eaeA*	Intimin	Major structural component of flagella; required for motility	[26]
	fliC	Flagellin	Pore-forming toxin with lytic activity	[27]
	hly	Enterohemolysin and α-hemolysin	Toxins with hemolytic activity	[27]
	ler	LEE1-encoded regulator	Transcriptional activator of the LEE pathogenicity island	[27]
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	[28]
Escherichia coli *Clostridium* spp. *Staphylococcus aureus*	*stx*	Shiga-like toxin Stx	Toxin causing diarrhea and other disorders	[28]
	tir	Translocated intimin protein	Adhesion to epithelial cells	[29]
		Adhesins	Adhesion on both abiotic and cell surfaces	[29]
		Intimin receptor EspE	Type III secretion system that allows attaching and effacing (A/E) lesions	[29]
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	[29]
	tcdA	Enterotoxin A	Enterotoxin causing fluid secretion and intestinal inflammation	[30]
	tcdB	Toxin B	Potent cytotoxin causing cytoskeletal damage	[6]
	txeR	σ factor	Alternative sigma factor regulating tcdA and tcdB expression	[17]
	agr		Quorum sensing system controlling toxin production	[22]
	ica		Polysaccharide intercellular adhesin for biofilm formation	[22]
Helicobacter spp.	*ndvB*		Involved in cyclic glucan synthesis and biofilm formation	[22]
	pil	Pilin	For twitching motility and adherence	[29]
	rhI/R	RhI/R protein	Transcriptional regulator in the RhI quorum sensing system	[30]

Table 1: *Summary of virulence genes affected by lactobacilli.*

Conclusion

In summary, probiotic food items and dietary supplements demonstrate significant efficacy in reducing the severity and incidence of various common forms of diarrhea. Substantial evidence supports their role in preventing antibiotic-associated diarrhea and acute infectious diarrhea caused by viral and bacterial pathogens. The therapeutic benefit of probiotics is attributed to their ability to help restore gut microbial balance, normalize stool consistency, and modulate the local immune response. While diarrhea is often a self-limiting condition characterized by loose, watery stools, it can lead to serious complications such as dehydration, particularly in vulnerable populations. It is crucial to seek medical attention if symptoms persist for more than two days in adults or appear immediately in young children, as children under five are at high risk for severe, rapid dehydration. Probiotics represent a safe, cost-effective strategy for the management and prevention of diarrheal illnesses, underscoring their value in both clinical and public health contexts.

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