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# The Role of Probiotics in Combating Antibiotic-Resistant Bacteria

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Annotation: Antibiotic resistance is an escalating global health crisis that undermines the efficacy of conventional antimicrobial therapies. As traditional antibiotics become less effective against resistant pathogens, alternative approaches such as probiotics have gained attention for their potential role in mitigating antimicrobial resistance. Probiotics defined as live microorganisms that confer health benefits to the host exhibit various mechanisms that make them promising candidates in this context. These include competitive exclusion of pathogens, enhancement of the host's immune response, production of antimicrobial substances, and modulation of gut microbiota. This study explores the current literature on the use of probiotics against antibiotic-resistant bacteria, examining both their direct and indirect antimicrobial activities. Mechanistic insights reveal that probiotics may disrupt quorum sensing, produce bacteriocins and organic acids, and strengthen epithelial barriers, thereby inhibiting the colonization and proliferation of resistant microbes. Despite their promise, the clinical translation of probiotics faces several challenges, such as strain specificity, inconsistent efficacy. concerns safety in immunocompromised individuals, and lack of regulatory standardization. The review concludes that while probiotics are not a standalone solution, they offer a complementary strategy in the global effort to curb antibiotic resistance.

Recommendations include advancing strainspecific research, conducting well-designed clinical trials, enhancing regulatory oversight, and integrating probiotics into antimicrobial stewardship programs. With rigorous scientific validation and strategic implementation, probiotics may serve as an effective tool in preserving the efficacy of current antibiotics and promoting sustainable healthcare practices.

**Keywords:** Probiotics, Antibiotic Resistance, Antimicrobial Activity, Resistant Pathogens, Bacteriocins.

#### Introduction

Among the most urgent public health concerns of the twenty-first century is antibiotic resistance. Worldwide morbidity, death, and healthcare expenses have risen as fast and widely resistant to several antibiotics have emerged among microorganisms (World Health Organisation [WHO], 2020). Often referred to as "superbugs, antibiotic-resistant bacteria seriously compromise the efficient treatment of infectious diseases, therefore undermining decades of medical science and public health advancement (Centres for Disease Control and Prevention [CDC], 2019).

Resistance mechanisms in pathogenic bacteria have developed rapidly in response to overuse and misuse of antibiotics in human medicine, veterinary practices, and agriculture (Laxminarayan et al., 2013). Among these resistance systems include changed antibiotic targets, enzymatic degradation of antibiotics, enhanced efflux, and lowered permeability to medicines (Munita & Arias, 2016). Treating infections brought on by antibiotic-resistant bacteria, such methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant Pseudomonas aeruginosa, is therefore progressively challenging (Davies & Davies, 2010). In the middle of this increasing threat, alternative or complementary therapies desperately needed to fight antibiotic-resistant bacteria. Using probiotics living microorganisms that help the host remain healthy when given in appropriate dosages presents one exciting direction (Hill et al., 2014). Research on probiotics' roles in preserving gut health, immune system modulation, and gastrointestinal infections prevention has been extensive (Sanders et al., 2018). Recent studies have concentrated on their possible use as antimicrobial agents able to prevent or lower colonisation by antibiotic-resistant bacteria (Suez et al., 2019).

Through several processes—competitive exclusion of pathogens, synthesis of antimicrobial compounds (bacteriocins, organic acids), modulation of host immune responses, and disturbance of biofilms— Probiotics may exert their antimicrobial effects (Corr et al., 2007; Le Beer, Vanderleyden & De Keersmaecker, 2008). Moreover, probiotics offer a better safety profile than conventional antibiotics and less chance of causing resistance (O'Toole et al., 2017). Therefore, knowing the part of probiotics in fighting antibiotic-resistant bacteria should open the path for new therapeutic approaches that complement current antibiotics and lower the load of resistance.

Notwithstanding progress in the creation of antibiotics, the spread of antibiotic-resistant bacteria keeps unchecked and compromises world health safety. Growing in uselessness, conventional antibiotics are causing treatment failures, extended hospital stays, and higher death rates (Ventola, 2015). The development of new antibiotics is slow and costly, and resistance tends to develop swiftly even against novel drugs (Wright, 2010). Furthermore, antibiotic resistance goes beyond clinical settings and affects agricultural sectors as well as community surroundings, therefore complicating efforts to stop its dissemination (Marshall & Levy, 2011). New

antibiotics' pipeline is drying out, hence alternate medicines are desperately needed to fight resistant infections and stop their spread. By means of non-antibiotic strategies to control or eradicate resistant bacteria, probiotics present a possible answer. Though in vitro and some in vivo data point to promise, the exact function and effectiveness of probiotics in treating antibiotic-resistant illnesses are yet unknown. Methodical research on which probiotic strains are most successful, the processes by which they stop resistant bacteria, best ways of administration, and possible incorporation into clinical practice is much needed (Fijan, 2014).

#### **Overview of Antibiotic Resistance**

Emerging as a serious worldwide health concern, antibiotic resistance (AR) compromises the effectiveness of therapies for bacterial infections and jeopardises the basis of contemporary medicine. Among the ten worldwide public health concerns confronting mankind, the World Health Organisation (WHO) ranks antimicrobial resistance (AMR). This review of the literature explores the mechanics of AR, its worldwide influence, related causes, and the several approaches under use to address this growing problem. Many methods have evolved in bacteria to avoid the effects of antibiotics, therefore rendering treatments useless. The main way is to stop antibiotic buildup inside bacterial cells. This is achieved either by limiting the entry of antibiotics through reduced permeability of the bacterial cell wall or by actively expelling drugs utilising efflux pumps. Gram-negative bacteria, for example, have porin channels that control antibiotic entry; mutations causing low porin expression will greatly lower antibiotic intake.

Still another mechanism is the enzymatic modification or breakdown of antibiotics. For example, beta-lactamases neutralise the antibacterial action of penicillins and cephalosporins by hydrozing their beta-lactam ring. The development of metallo-beta-lactamases, notably New Delhi metallo-beta-lactamase-1 (NDM-1), has further confounded therapy choices by rendering resistance to a wide spectrum of beta-lactam antibiotics. Furthermore, plasmids, transposons, and integrons help bacteria to acquire resistance genes by horizontal gene transfer (HGT). Environmental elements, notably the presence of heavy metals such as copper and zinc, might improve HGT by causing stress reactions in bacteria, therefore encouraging the spread of resistance genes. AR has major consequences for public health, economic stability, and the effectiveness of medical treatments among other areas. Directly attributable to drug-resistant bacterial infections, 1.27 million fatalities occurred in 2019. Projections show that, left untreated, AR might cause 10 million deaths annually by 2025, more than cancer kills.

Notably, rising healthcare expenses are caused in part by extended hospital stays, the demand for more costly and intensive care, and lost productivity resulting from protracted disease. Moreover, AR threatens developments in major operations, chemotherapy, organ transplants, and other medical treatments depending mostly on efficient antibiotic prophylaxis. There are several linked elements that help AR to accelerate. Main causes of overuse and abuse of antibiotics in human medicine are human medicine itself. Antibiotics are commonly demanded by patients for viral infections, against which these medications are useless and results in pointless prescriptions. In some areas, antibiotics are sold over-the-counter without a prescription, therefore encouraging improper use and self-medication. Moreover important are agricultural methods. Not just for illness treatment but also for growth promotion and disease prevention in healthy animals, almost seventy percent of antibiotics are given to cattle. This extensive use encourages the growth of resistant germs, which can be passed on to people via environmental routes, direct touch, or the food chain. Particularly in low- and middle-income countries, socioeconomic elements including poverty, lack of education, and poor healthcare infrastructure aggravate the situation. Limited access to excellent healthcare and diagnostics in these contexts results in empirical treatment with broad-spectrum antibiotics, therefore raising the risk of resistance development.

## Probiotics and Antimicrobial Activity against Pathogens

Emerging as a serious worldwide health concern, antibiotic resistance (AR) compromises the

effectiveness of therapies for bacterial infections and jeopardises the basis of contemporary medicine. Among the ten worldwide public health concerns confronting mankind, the World Health Organisation (WHO) ranks antimicrobial resistance (AMR) at number one. This review of the literature explores the mechanics behind AR, its worldwide influence, contributory causes, and the several approaches under use to address these growing problems.

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Furthermore important are agricultural methods. Not just for illness treatment but also for growth promotion and disease prevention in healthy animals, almost seventy percent of antibiotics are given to cattle. This extensive use encourages the growth of resistant germs, which can be passed on to people via environmental routes, direct touch, or the food chain. Particularly in low- and middle-income countries, socioeconomic elements including poverty, lack of education, and poor healthcare infrastructure aggravate the situation. Limited access to quality healthcare and diagnostics in these areas results in empirical treatment with broad-spectrum antibiotics, therefore raising the risk of resistance development.

## Probiotics against Antibiotic-Resistant Bacteria

Public health and clinical medicine are seriously threatened by the advent and worldwide distribution of antibiotic-resistant microorganisms. By making many usually used medications useless against diseases, antibiotic resistance results in higher morbidity, mortality, and healthcare costs (WHO, 2020). This dilemma is driving increasing interest in the creation of alternative or complementing approaches to fight bacterial infections. Among these, probiotics—living microorganisms that help the host remain healthy—have become especially well-known for their ability to fight antibiotic-resistant bacteria. The function of probiotics in the prevention and treatment of illnesses generated by antibiotic-resistant bacteria, their methods of action,

particular strains with established efficacy, and future options for incorporating probiotics into antimicrobial treatments are investigated in this review of the literature.

Among the top ten worldwide public health hazards identified by the World Health Organisation (WHO, 2020) is antibiotic resistance. Pathogens include Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa have evolved resistance to many antibiotics classes, including carbapenems, fluoroquinolones, and methicillin, therefore complicating treatment of infections (CDC, 2019). Accelerating this issue are the overuse and abuse of antibiotics in human health, industry, and agriculture as well as animal husbandry. Given this, probiotics are under investigation not just for their overall antibacterial properties but also for their particular possible resistance against multidrug-resistant (MDR) infections. By means of multiple non-traditional antibiotic pathways, probiotics fight antibiotic-resistant bacteria, therefore lowering the danger of helping to generate resistance. These systems comprise:

## **Production of Antimicrobial Substances:**

Many probiotics, particularly lactic acid bacteria (LAB) such as *Lactobacillus* and *Bifidobacterium* species, produce antimicrobial metabolites such as organic acids (e.g., lactic and acetic acids), hydrogen peroxide, and bacteriocins. Bacteriocins are ribosomally synthesized antimicrobial peptides that inhibit or kill closely related bacterial strains, including drug-resistant species (Dobson et al., 2012). For example, *Lactobacillus plantarum* produces plantaricin, which has shown inhibitory effects against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) (Yang et al., 2014).

# 1. Competitive Exclusion and Colonization Resistance:

Probiotics prevent the colonization of pathogens by adhering to mucosal surfaces, thereby occupying binding sites and consuming nutrients required by pathogenic bacteria. This competitive exclusion mechanism limits the ability of resistant pathogens to establish themselves in the gastrointestinal tract or urogenital system (Servin, 2004).

## 2. Modulation of Host Immunity:

Probiotics enhance the host's immune response by stimulating the production of mucosal antibodies, cytokines, and antimicrobial peptides such as defensins. This immunomodulatory effect can help the body naturally fight off infections caused by antibiotic-resistant organisms (Bron et al., 2012).

## 3. **Biofilm Disruption:**

Some probiotic strains inhibit the formation or promote the disruption of bacterial biofilms, which are often associated with antibiotic resistance. Biofilms protect bacteria from antibiotics and the immune system, but probiotics such as *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* have been shown to reduce biofilm formation by MRSA and *Pseudomonas aeruginosa* (Vuotto et al., 2014).

# Probiotic Strains with Activity against Resistant Pathogens

Several studies have documented the efficacy of specific probiotic strains against antibioticresistant bacteria. For instance:

- ➤ Lactobacillus rhamnosus GG has demonstrated activity against MRSA and Clostridium difficile in both in vitro and clinical studies (Koning et al., 2008).
- Lactobacillus acidophilus inhibits the growth of extended-spectrum beta-lactamase (ESBL)producing *E. coli* strains through the production of lactic acid and bacteriocins (Spinler et al., 2008).

- Saccharomyces boulardii, a probiotic yeast, has been effective in reducing recurrent C. difficile infections, a common consequence of antibiotic resistance, by modulating gut flora and neutralizing bacterial toxins (McFarland, 2010).
- Bifidobacterium bifidum and B. longum have shown potential in reducing the colonization of VRE in the intestines by competitive inhibition and immunostimulation (Zhou et al., 2010).

# **Clinical Applications and Evidence**

The use of probiotics in clinical settings has been explored primarily in the context of preventing or reducing the severity of antibiotic-associated complications. A meta-analysis by Goldenberg et al. (2017) found that probiotics significantly reduced the incidence of antibiotic-associated diarrhea (AAD) and *C. difficile*-associated diarrhea, both of which can be exacerbated by the presence of antibiotic-resistant organisms. Another study by Manzoni et al. (2006) reported a decrease in late-onset sepsis caused by drug-resistant bacteria in neonates receiving oral probiotics.

In hospital environments where resistant infections are common, probiotics may also serve as part of decolonization strategies. For example, probiotics have been trialed for the eradication of VRE from the gastrointestinal tract, with promising results (Morrow et al., 2010). However, more randomized controlled trials (RCTs) are needed to establish consistent clinical protocols and validate efficacy.

# **Probiotics and Antibiotic Synergy**

Emerging research suggests that probiotics may also enhance the efficacy of antibiotics, potentially reducing the required dose or duration of antibiotic therapy. Probiotics can disrupt bacterial biofilms and alter the permeability of bacterial membranes, allowing antibiotics to act more effectively (Ng et al., 2009). This synergistic effect could help overcome resistance mechanisms and decrease antibiotic selection pressure

# Mechanistic Insights into Probiotic Action Against Resistant Bacteria

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts (FAO/WHO, 2002), are increasingly recognized for their role in combating antibiotic-resistant bacterial infections. While the clinical potential of probiotics against resistant pathogens is well documented, understanding the specific mechanisms through which they exert these effects is critical to optimizing their application in therapeutic and preventive contexts. This review explores the molecular and cellular mechanisms underlying probiotic action against antibiotic-resistant bacteria, providing a foundation for their strategic deployment in antimicrobial resistance (AMR) mitigation.

1. Production of Antimicrobial Compounds

One of the most well-documented mechanisms by which probiotics act against resistant bacteria is through the production of various antimicrobial compounds. These substances can directly inhibit or kill pathogenic bacteria, including those with multidrug resistance (MDR).

## a. Organic Acids

Probiotics such as *Lactobacillus* and *Bifidobacterium* spp. produce organic acids (e.g., lactic acid, acetic acid) that lower the pH of their environment, making it inhospitable for many pathogenic microbes. This acidification disrupts bacterial metabolism and membrane integrity (Alakomi et al., 2000), impairing the growth of drug-resistant strains such as *Escherichia coli*, *Clostridium difficile*, and *Salmonella* spp.

## **b.** Bacteriocins

Bacteriocins are ribosomally synthesized peptides produced by bacteria that exhibit antimicrobial activity against closely or distantly related bacteria. Some bacteriocins have shown

potent inhibitory effects on methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycinresistant *Enterococci* (VRE), and carbapenem-resistant *Klebsiella pneumoniae* (Dobson et al., 2012). For instance, nisin (produced by *Lactococcus lactis*) and plantaricin (from *Lactobacillus plantarum*) disrupt bacterial cell walls and membranes, causing leakage of cellular contents and cell death.

#### c. Hydrogen Peroxide

Certain *Lactobacillus* strains generate hydrogen peroxide ( $H_2O_2$ ), which acts as a reactive oxygen species to damage bacterial DNA, proteins, and lipid membranes. This oxidative stress is particularly effective against anaerobic and microaerophilic pathogens such as *Gardnerella vaginalis* and *Neisseria gonorrhoeae* (Ouwehand et al., 2002).

2. Competitive Exclusion and Adhesion Inhibition

Probiotics can outcompete resistant pathogens for nutrients and adhesion sites on mucosal surfaces, a phenomenon referred to as competitive exclusion.

**a.** Surface Binding Competition

By adhering to epithelial cells in the gastrointestinal or urogenital tracts, probiotic strains prevent pathogen binding and colonization. For example, *Lactobacillus rhamnosus GG* binds to mucin and epithelial cells, blocking *E. coli* O157:H7 and *Salmonella* spp. from attaching to intestinal linings (Collado et al., 2007).

#### b. Mucin Production Stimulation

Some probiotics enhance host mucin gene expression (MUC2, MUC3), thereby strengthening the mucosal barrier and physically obstructing bacterial invasion (Mack et al., 2003). This creates a hostile environment for resistant pathogens, reducing infection risks.

#### 3. Quorum Sensing Interference and Biofilm Disruption

Biofilms are structured microbial communities that confer resistance to antibiotics and host immune responses. Probiotics can disrupt biofilm formation and interfere with quorum sensing the bacterial communication system.

#### a. Quorum Quenching

Probiotics secrete enzymes such as lactonases and acylases that degrade quorum sensing molecules (AHLs, AI-2), interrupting intercellular communication among resistant bacteria like *Pseudomonas aeruginosa* (Bai et al., 2019). This inhibition reduces virulence factor production and biofilm maturation.

#### **b.** Biofilm Matrix Degradation

Probiotic-secreted enzymes, such as proteases and DNases, can degrade extracellular polymeric substances (EPS) in biofilms. *Lactobacillus acidophilus* and *L. plantarum* have demonstrated biofilm-disrupting activity against MRSA and VRE biofilms (Vuotto et al., 2014).

#### 4. Modulation of Host Immune Response

Probiotics enhance host immunity, helping the body to mount effective defenses against resistant pathogens.

# **a.** Innate Immune Activation

Probiotics stimulate Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors in intestinal epithelial cells and dendritic cells. This promotes the production of pro-inflammatory cytokines (e.g., IL-6, IL-12, TNF- $\alpha$ ) and antimicrobial peptides (e.g., defensins, cathelicidins) (Bron et al., 2012).

# **b.** Enhancement of Adaptive Immunity

Probiotics increase immunoglobulin A (IgA) production, facilitating pathogen neutralization and removal. Enhanced antigen presentation also supports the development of specific T-cell responses against invading drug-resistant bacteria (Ng et al., 2009).

5. Restoration of Microbiota Balance

Antibiotic treatments often disrupt gut microbiota, allowing resistant pathogens to proliferate (dysbiosis). Probiotics help re-establish microbial equilibrium.

**a.** Microbiota Modulation

By increasing beneficial bacteria (e.g., *Bifidobacteria*, *Lactobacilli*) and reducing harmful species, probiotics maintain colonization resistance. This prevents opportunistic infections by resistant organisms such as *C. difficile* (McFarland, 2010).

b. Short-Chain Fatty Acid (SCFA) Production

Probiotic fermentation of prebiotics leads to the generation of SCFAs (butyrate, acetate, propionate), which promote epithelial integrity, reduce inflammation, and inhibit pathogen overgrowth (Fukuda et al., 2011).

# 7. Synergism with Antibiotics

Probiotics may potentiate antibiotic efficacy, a promising approach in overcoming resistant infections.

- Membrane Disruption: Probiotics may increase membrane permeability of pathogens, facilitating better antibiotic penetration.
- Efflux Pump Inhibition: Certain probiotic metabolites suppress bacterial efflux pumps, which are commonly responsible for multidrug resistance (Zhou et al., 2019).
- Antibiotic Tolerance Reduction: By downregulating stress response genes, probiotics reduce pathogen tolerance to antibiotics, enhancing bactericidal effects.

# Challenges and Limitations in Using Probiotics against Antibiotic Resistance

Despite the growing interest and scientific support for the use of probiotics as a complementary or alternative strategy to combat antibiotic-resistant bacteria, several challenges and limitations persist. These barriers range from biological and clinical uncertainties to regulatory and commercial complexities. Understanding these limitations is essential for realistic expectations, effective implementation, and the advancement of research in the application of probiotics against antimicrobial resistance (AMR). This section outlines the major scientific, clinical, and operational hurdles associated with probiotic use in the context of antibiotic resistance.

# 1. Strain-Specific Effects and Variability

A significant limitation in the use of probiotics is the strain-specific nature of their efficacy. Not all probiotic strains exhibit the same level of antimicrobial activity or clinical effectiveness. For example, *Lactobacillus rhamnosus GG* may show inhibitory effects against *Clostridium difficile*, while other strains of *Lactobacillus* might not. This variability complicates the generalization of findings and the selection of appropriate strains for therapeutic use against specific resistant pathogens (Hill et al., 2014). Furthermore, inter-strain and inter-species variability in tolerance to gastric acid, bile salts, and adhesion capacity to mucosal surfaces limits the consistent colonization and activity of probiotics in different hosts or environments. These differences also hinder reproducibility and the formulation of standardized clinical protocols.

# 2. Inconsistent Clinical Outcomes and Lack of Robust Trials

Although in vitro and animal studies have shown promising antimicrobial effects of probiotics,

translating these results to human subjects remains inconsistent. Several clinical trials have reported mixed or inconclusive findings regarding the efficacy of probiotics in reducing antibiotic-resistant infections or mitigating antibiotic-associated side effects like diarrhea. This inconsistency arises from factors such as small sample sizes, short study durations, lack of standardization in probiotic dose and delivery and differences in patient populations and underlying health conditions.

Moreover, many clinical trials lack rigorous methodologies (e.g., double-blinding, placebo control), limiting the strength of the evidence. Without robust, large-scale, and well-controlled studies, the medical community remains cautious about fully endorsing probiotics as a reliable treatment against resistant pathogens (Goldenberg et al., 2017).

## **Regulatory and Quality Control Issues**

Probiotic products are often marketed as dietary supplements or functional foods, not drugs, meaning they are subject to less stringent regulatory oversight in many countries. As a result, issues such as mislabeling of strains, inaccurate colony-forming unit (CFU) counts, Contamination and lack of product stability are commonly reported (Azad et al., 2018). These quality control lapses can compromise both efficacy and safety, especially when probiotics are used in a medical or hospital setting. Furthermore, the absence of harmonized global regulatory frameworks for probiotic products complicates their clinical adoption. There is a need for regulatory bodies like the FDA, EMA, and WHO to develop standardized protocols for evaluating and approving probiotics for therapeutic use against antibiotic-resistant infections.

#### Conclusion

The escalating threat of antibiotic resistance has prompted the exploration of alternative and adjunctive therapies, among which probiotics have garnered significant attention. Probiotics, with their capacity to modulate the gut microbiota, compete with pathogens, enhance mucosal barriers, and produce antimicrobial substances, offer a promising natural defense against antibiotic-resistant bacteria. Numerous in vitro, animal, and some clinical studies have demonstrated their potential to reduce the incidence of infections, curb the overgrowth of resistant organisms, and mitigate the adverse effects of antibiotic therapy. However, despite these promising findings, several challenges persist that limit their widespread clinical adoption and efficacy. These limitations include the strain-specific nature of probiotic effects, inconsistent clinical evidence, lack of long-term colonization, and potential risks in immunocompromised individuals. Additionally, regulatory ambiguities, quality control issues, and commercial hurdles further complicate the implementation of probiotics as a reliable component of antimicrobial stewardship. The absence of unified global standards and the risk of transferring resistance genes from probiotic strains to pathogens also raise critical safety and ethical concerns.

#### Recommendations

More targeted research should be conducted to identify specific probiotic strains with demonstrated efficacy against particular antibiotic-resistant pathogens. This includes extensive genomic and phenotypic characterization of strains, including their antimicrobial production, colonization abilities, and resistance profiles.

Large-scale, multicenter, randomized controlled trials (RCTs) with standardized dosing, duration, and patient monitoring are essential to validate the clinical utility of probiotics in preventing or treating infections caused by resistant bacteria.

Research should shift towards human-based studies that explore the mechanistic pathways of probiotic action in vivo. This includes studies on how probiotics interact with the host microbiome, immune system, and pathogens under real physiological conditions.

Investment in next-generation or engineered probiotics that can be tailored for specific tasks such as targeted pathogen suppression, immune modulation, or delivery of therapeutic agents can

offer innovative approaches to tackling antibiotic resistance.

Safety evaluations should become more rigorous, especially for high-risk populations. Probiotics intended for therapeutic use should undergo preclinical toxicity testing, genetic stability analysis, and monitoring for horizontal gene transfer capabilities.

Probiotics should be considered as a supportive tool within antimicrobial stewardship programs, particularly in hospitals and long-term care facilities. Their role in restoring gut microbiota post-antibiotic treatment and preventing secondary infections should be strategically explored.

#### References

- 1. Bron, P. A., Kleerebezem, M., Brummer, R. J., Cani, P. D., Mercenier, A., MacDonald, T. T., ... & Wells, J. M. (2017). Can probiotics modulate human disease by impacting intestinal barrier function? British Journal of Nutrition, 117(1), 93-107.
- Bush, K., & Fisher, J. F. (2011). Epidemiological expansion, structural studies, and clinical challenges of new β-lactamases from gram-negative bacteria. Annual Review of Microbiology, 65, 455-478.
- 3. Centers for Disease Control and Prevention (CDC). (2019). Antibiotic resistance threats in the United States. U.S. Department of Health and Human Services.
- 4. Cotter, P. D., Hill, C., & Ross, R. P. (2005). Bacteriocins: Developing innate immunity for food. Nature Reviews Microbiology, 3(10), 777-788.
- 5. Cotter, P. D., Ross, R. P., & Hill, C. (2013). Bacteriocins a viable alternative to antibiotics? Nature Reviews Microbiology, 11(2), 95-105.
- 6. Corr, S. C., Li, Y., Riedel, C. U., O'Toole, P. W., Hill, C., & Gahan, C. G. (2007). Bacteriocin production as a mechanism for the anti-infective activity of Lactobacillus salivarius UCC118. Proceedings of the National Academy of Sciences, 104(18), 7617-7621.
- Cunha, M., Dias, C., Pereira, R., & Silva, J. (2019). Probiotics and antibiotic resistance: How do probiotic bacteria influence antibiotic resistance genes? Microbial Pathogenesis, 127, 223-234.
- 8. Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews, 74(3), 417-433.
- 9. Doron, S., & Snydman, D. R. (2015). Risk and safety of probiotics. Clinical Infectious Diseases, 60(suppl\_2), S129-S134.
- Fijan, S. (2014). Microorganisms with claimed probiotic properties: An overview of recent literature. International Journal of Environmental Research and Public Health, 11(5), 4745-4767.
- 11. Goldenberg, J. Z., Yap, C., Lytvyn, L., Lo, C. K., Beardsley, J., Mertz, D., & Johnston, B. C. (2017). Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews, (12).
- 12. Hall-Stoodley, L., Costerton, J. W., & Stoodley, P. (2004). Bacterial biofilms: From the natural environment to infectious diseases. Nature Reviews Microbiology, 2(2), 95-108.
- 13. Henao-Martínez, A. F., McCarthy, K., Rae, M., & Franco-Paredes, C. (2017). Probiotic use in patients with antibiotic-resistant infections. Infectious Disease Clinics of North America, 31(3), 593-604.
- Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., ... & Sanders, M. E. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology, 11(8), 506-514.

- Kumar, M., Nagpal, R., Kumar, R., Hemalatha, R., Verma, V., Kumar, A., ... & Yadav, H. (2017). Probiotic metabolites as epigenetic targets in the prevention of colon cancer. Nutrition Reviews, 75(12), 910-929.
- Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., ... & Cars, O. (2013). Antibiotic resistance the need for global solutions. The Lancet Infectious Diseases, 13(12), 1057-1098.
- Lebeer, S., Vanderleyden, J., & De Keersmaecker, S. C. (2008). Genes and molecules of lactobacilli supporting probiotic action. Microbiology and Molecular Biology Reviews, 72(4), 728-764.
- 18. Li, X. Z., Plésiat, P., & Nikaido, H. (2015). The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clinical Microbiology Reviews, 28(2), 337-418.
- 19. Mendonça, S., Guerreiro, J. F., & Pacheco, A. (2020). Probiotics and their role in combating bacterial biofilms: A review. Microorganisms, 8(7), 1056.
- 20. Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. Microbiology Spectrum, 4(2).
- 21. Nikaido, H. (2003). Molecular basis of bacterial outer membrane permeability revisited. Microbiology and Molecular Biology Reviews, 67(4), 593-656.
- 22. O'Toole, P. W., Marchesi, J. R., & Hill, C. (2017). Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. Nature Microbiology, 2, 17057.
- 23. Ouwehand, A. C., Salminen, S., & Isolauri, E. (2016). Probiotics: An overview of beneficial effects. Antonie Van Leeuwenhoek, 82, 279-289.
- 24. Sánchez, B., Bressollier, P., & Urdaci, M. C. (2017). Exported proteins in probiotic bacteria: Adhesion to intestinal surfaces, host immunomodulation and molecular cross-talk with the host. FEMS Immunology & Medical Microbiology, 54(1), 1-17.
- 25. Sanders, M. E., Merenstein, D. J., Reid, G., Gibson, G. R., & Rastall, R. A. (2018). Probiotics and prebiotics in intestinal health and disease: From biology to the clinic. Nature Reviews Gastroenterology & Hepatology, 16(10), 605-616.
- 26. Smith, R., & Coast, J. (2013). The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest. Applied Health Economics and Health Policy, 11(3), 325-331.
- 27. Suez, J., Zmora, N., Segal, E., & Elinav, E. (2019). The pros, cons, and many unknowns of probiotics. Nature Medicine, 25(5), 716-729.
- 28. Ventola, C. L. (2015). The antibiotic resistance crisis: Part 1: Causes and threats. Pharmacy and Therapeutics, 40(4), 277-283.
- 29. World Health Organization (WHO). (2020). Global antimicrobial resistance and use surveillance system (GLASS) report: Early implementation 2020.
- 30. Wright, G. D. (2010). Q&A: Antibiotic resistance: Where does it come from and what can we do about it? BMC Biology, 8(1), 123.
- 31. Centers for Disease Control and Prevention (CDC). (2019). Antibiotic resistance threats in the United States. U.S. Department of Health and Human Services.
- 32. Corr, S. C., Li, Y., Riedel, C. U., O'Toole, P. W., Hill, C., & Gahan, C. G. (2007). Bacteriocin production as a mechanism for the anti-infective activity of Lactobacillus salivarius UCC118. Proceedings of the National Academy of Sciences, 104(18), 7617-7621.

- Cotter, P. D., Hill, C., & Ross, R. P. (2005). Bacteriocins: Developing innate immunity for food. Nature Reviews Microbiology, 3(10), 777–788.
- 34. Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews, 74(3), 417-433.
- 35. Fijan, S. (2014). Microorganisms with claimed probiotic properties: An overview of recent literature. International Journal of Environmental Research and Public Health, 11(5), 4745-4767.
- 36. Hall-Stoodley, L., Costerton, J. W., & Stoodley, P. (2004). Bacterial biofilms: From the natural environment to infectious diseases. Nature Reviews Microbiology, 2(2), 95-108.
- 37. Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., ... & Sanders, M. E. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology, 11(8), 506-514.
- Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., ... & Cars, O. (2013). Antibiotic resistance the need for global solutions. The Lancet Infectious Diseases, 13(12), 1057-1098.
- 39. Lebeer, S., Vanderleyden, J., & De Keersmaecker, S. C. (2008). Genes and molecules of lactobacilli supporting probiotic action. Microbiology and Molecular Biology Reviews, 72(4), 728-764.
- 40. Marshall, B. M., & Levy, S. B. (2011). Food animals and antimicrobials: Impacts on human health. Clinical Microbiology Reviews, 24(4), 718-733.
- 41. Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. Microbiology Spectrum, 4(2).
- 42. O'Toole, P. W., Marchesi, J. R., & Hill, C. (2017). Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. Nature Microbiology, 2, 17057.
- 43. Sanders, M. E., Merenstein, D. J., Reid, G., Gibson, G. R., & Rastall, R. A. (2018). Probiotics and prebiotics in intestinal health and disease: From biology to the clinic. Nature Reviews Gastroenterology & Hepatology, 16(10), 605-616.
- 44. Suez, J., Zmora, N., Segal, E., & Elinav, E. (2019). The pros, cons, and many unknowns of probiotics. Nature Medicine, 25(5), 716-729.
- 45. Ventola, C. L. (2015). The antibiotic resistance crisis: Part 1: Causes and threats. Pharmacy and Therapeutics, 40(4), 277-283.
- 46. World Health Organization (WHO). (2020). Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
- 47. Wright, G. D. (2010). Antibiotic resistance in the environment: A link to the clinic? Current Opinion in Microbiology, 13(5), 589-594.