From Gut Health to Global Health: The Probiotic Solution to Antibiotic Resistance

Sabeeka Sajjal[1,*], Muhammad Tayyab[2], Saadit Rasool[3], Hasham Ali Khan[4], Nida Kanwal[5], Eman[6], Tooba Saleem[7] and Muhammad Irfan Shah[8]

[1]Institute of Microbiology, University of Agriculture Faisalabad, Pakistan
[2]Department of Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[3]Institute of Microbiology, University of Agriculture Faisalabad, Pakistan
[4]Centre for Biotechnology and Microbiology, University of Swat, Swat, Pakistan
[5]Department of Food Science and Technology, Riphah International University, Faisalabad, Pakistan
[6]Institute of Microbiology and Molecular Genetics, Punjab University, Lahore, Pakistan
[7]Institute of Microbiology and Molecular Genetics, Punjab University, Lahore, Pakistan
[8]Institute of Microbiology, University of Agriculture Faisalabad, Faisalabad, Pakistan
*Corresponding author: sabeekasajal@gmail.com

Abstract

Antibiotic resistance is a recurring threat to world health. The antimicrobial issue is a global issue that causes elevation in mortality and morbidity rates. The first target of antibiotics is frequently the gut flora. The constant fight against bacterial infections and other diseases associated with it is difficult, and the ineffective preventative strategies, lack of medication strategies, and very few novel antibiotics that can be used in clinical trials will necessitate substitute antimicrobial therapies and lead to the creation of new treatment plans. Alternative strategies should also be considered; probiotics may be useful in this situation. Probiotics have been shown in both human and veterinary medicine to lower the risk of infectious illnesses. Stabilizing the gut microbiota is one of the processes through which probiotics are thought to have this impact. Generally, *Lactobacillus* and *Lactococcus* have members in them that are designated as Generally Regarded as Safe (GRAS) or Qualified Presumption of Safety (QPS). It has been noted that taking probiotics along with antibiotics can lessen the incidence, severity, and duration of several diseases. Although the precise amount to which probiotics can directly stop the emergence of antibiotic resistance is not yet being studied completely, using antibiotics while preserving a balanced microbiota may undoubtedly present opportunities to stop the spread of antibiotic resistance.

Keywords: Public health, Antibiotic resistance, ARGs, *Lactobacillus*, Probiotics, AAD

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Introduction

Among the most significant medical advancements, antibiotics have greatly aided in the diagnosis, treatment, and containment of infectious infections. A global health challenge, antibiotic resistance, involves resistance-related bacteria and their gene transfer among animals, humans, and the environment (Larsson and Flach, 2022). Unfortunately, the widespread and particularly inappropriate use of them has contributed to the growth of antibiotic resistance (Dache et al., 2021). Concerns have been raised about the benefit of antibiotics in human medicine. Reducing the inappropriate use of antibiotics on both human and veterinary sides is the first step towards stopping the emergence of antibiotic resistance. Alternative strategies should also be considered; probiotics may be useful in this situation. Probiotics have been shown in both human and veterinary medicine to lower the risk of infectious illnesses (Tegegne and Kebede, 2022) thereby potentially reducing the need for antibiotics. Highly indicated usage of probiotics is in the case of antibiotic-associated diarrhea (AAD), which is one of the side effects of inappropriate antibiotic usage, found in up to 30% of hospitalized patients (Kopacz and Phadtare, 2022). Stabilizing the gut microbiota is one of the processes through which probiotics are thought to have this impact. Probiotics may also slow the development of antibiotic resistance through this route. Global organizations, including the World Health Organization (WHO) and the Centers for Disease (CDC), have recognized the growing threat of antibiotic-resistant bacteria to public health. An estimated 2.8 million antibiotic-resistant illnesses and 35,000 fatalities are reported in the US each year. The number of novel pharmacological treatments under development is still quite minimal, despite the fact that new antimicrobial therapeutics are still being researched. The fight against multidrug-resistant (MDR) microorganisms will require new tactics (CDC, 2019).

The scientific community is becoming more and more interested in the study of the microbiome which involves commensal bacteria of the gut (Lin et al., 2021). Further studies have been carried out which aimed to investigate the function of the microbiome in infection as well as in growth and development at the immunological and neurological levels, and its influence on inflammatory illnesses (Tavakoli et al., 2021). Human health is influenced by the enteric microbiome, and the enteric microbiome can influence human health in return. The intestinal microbiome is influenced by a variety of natural and external factors, like animal byproducts, dietary fiber, and exposure to environmental microbiology through soil and water sources (Cholewińska et al., 2021). The maternal microbiome is frequently the first source of inoculation, and it has the potential to affect the newborn microbiome as well as during the prenatal stage (Xiao and Zhao, 2023).

Among the most significant medications now used in modern medicine are antibiotics, which have made it possible to treat infections that would otherwise be fatal. Antibiotic usage is a major contributor to the iatrogenic effect and can cause disruptions to this complex system. The microbial colonies in our guts can undergo long-lasting alterations even after short-term antibiotic treatments or from antibiotics found in human food sources (Mercer and Arrieta, 2023). Pathogen colonization may occur when external stresses, such as antibiotics or dietary modifications, disturb the usual commensal flora. These pathogens carry their own ARGs (antimicrobial resistance genes), as the commensal bacteria present currently. The ARGs found in normal commensal flora can be acquired throughout the course of a lifetime exposure to various conditions, such as selective antibiotic pressure, or they can be present from birth (Li et al., 2019). The word "resistome" refers to the collection of all ARGs inside a microbiome; however, the genetic exchange of antibiotic resistance genes (ARGs) is carried out due to environment provided by complex nature of human microbiome which allows its transmission to pathogens from commensal microorganisms. The burden of these pathogens can be potentially reduced by targeting the resistome and intestinal microbiome as MDR infections become a greater threat to global health (Uddin et al*.,* 2021). Use of probiotics, prebiotics, and symbiotics provide an economical and safe way to modify diet and lessen the detrimental effects of multi-drug-resistant organisms on human health (Habteweld and Asfaw, 2023).

Antibiotics Side Effects on Microbiota

Since the 1940s, when antibiotics were widely used, research on the specific effects of antibiotics on pathogens has been mainly focused. But in the past ten years, its effect on the host microbiota has also been studied (Patangia et al., 2022). Human health is greatly influenced by the resident microbiota and the genes that correlate to it, or the microbiome, this is cleared due to developments in high-throughput sequencing technologies (Kanangat and Skaljic, 2021). The composition of the microbiota at the community level is determined by DNA sequencing-based techniques that use phylogenetic biomarkers like the 16S rRNA gene. Meanwhile, the functional potential of human microbiome has been highlighted after the study of metagenomics, which involves sequencing all of the genetic material of microorganisms in a sample, and metabolomics, which analyzes metabolites in a sample using mass spectrometry. The complexity and significance of balanced interactions between a host and its microbiota are also starting to become clear due to these new technologies (Aggarwal et al., 2022).

A disrupted microbiome has been related to several harmful health disorders, including obesity, metabolic syndrome, antibiotic-associated diarrhea (AAD), and irritable bowel illness. The diversity, composition, and resilience of microbial communities are the main ecological effects of antibiotics on our microbiota (Amor and Gore, 2022). Antibiotic classes and individual differences influence the degree of microbiome disturbance brought on by long- and short-term antibiotic treatment (Wang et al., 2022). Although this disruption usually happens quickly, and people start to return to normal soon after the antibiotic course is over. Due to the immature and developing microbiome and multiple courses of antibiotics in infants in their early life, they become more vulnerable to negative effects of long-term antibiotic usage which cause disruption of gut community for a long time (Ainonen et al., 2022).

This gut dysbiosis can further lead to such conditions in which an opportunistic bacteria like *Clostridium difficile*, one of the main causes of AAD, can grow (Pal et al., 2023). Transfer therapies of probiotics and microbiota, provide resistance against colonization and growth of pathogens which cause AAD and restore lost gut microbial diversity. It has been demonstrated that certain probiotic bacterial strains reduce the incidence and symptoms of AAD. Probiotic supplementation shows an effect, according to the dose given, on severe symptoms and incidence of antibiotic-associated diarrhea (Goodman et al., 2021). Even though the patients' microbiome profiles varied because of factors like antibiotic use, age, gender, and type of illness, the onset of AAD quickly caused a change in the fecal microbiota's composition. The negative impact of antibiotic therapy on human microbiota is frequently abrupt and severe, many people finish brief courses of antibiotics without experiencing any noticeable side effects, and the alteration in gut microbiota due to the effects of this antibiotic therapy remain poorly understood (Goodman et al., 2021).

Antibiotic Resistance

Certain molecular targets within the microbial cell are disrupted by antibiotics. Different bacteria may have altered or absent targets, which makes them resistant; this type of resistance known as intrinsic resistance, is shared by the majority or all strains within a species. But it can also be extrinsic (learned) in this case, several processes might be involved (Solanki and Das, 2024). An otherwise susceptible bacteria may become resistant to antibiotics due to a mutation in a gene that codes for an antibiotic's target. Comparably, a bacterium's susceptibility to some drugs, like intracellular antibiotics, may decrease or even become resistant due to a mutation in its (antibiotics') transport mechanism. Additionally, it is believed that this type of resistance is not transferable, except for daughter cells (Skowron et al., 2021).

Antibiotic resistance is a recurring danger to world health (Larsson and Flach, 2022). The development of educational programs, treatments, political objectives, and legislative efforts are the steps needed to slow down the increasing rate of antibiotic resistance. The challenge of decreasing the resistance of antibiotics, in a period where there are few novel therapies for bacteria-related infections, comes in front of researchers, legislators, and prescribers. The authors suggest that innovative medicines, policy, surveillance, and monitoring give answers to antibiotic resistance in agricultural and human domains. Due to the complex nature of antibiotic resistance, a multifaceted approach is needed to improve and attain desired outcomes in health care (Shedeed, 2024).

There is high morbidity and mortality rates due to antimicrobial resistance which has become a global issue. Different gram-negative and gram-positive bacteria causes infections which are incurable by traditional antimicrobials, is due to multidrug resistance patterns of these bacteria. In healthcare settings, broad-spectrum antibiotics are used unnecessarily because pathogenic bacteria are not identified in early stages of infection and antimicrobial susceptibility patterns in patients are not known which have bacteremia and other infections. Dramatic rise in resistance along with inadequate infection-control procedures, cause fast spread of resistant bacteria to the other patients and their surrounding area. Recent epidemiological data on antibiotic resistance on most frequently encountered infections caused by bacteria is available that will help to develop an efficient antimicrobial stewardship program in hospitals and help in decision making about new treatment options (Rhee et al., 2020).

It's a concerning topic that bacterial pathogens are becoming resistant to basic antibiotic therapy and rate of MDR are also emerging day by day. With each passing day it becomes difficult to fight against the infections and other diseases caused by these pathogens, and ineffective preventative strategies, a few novel antibiotics used in clinical trials, and inadequacy of effective medications arose the need for innovative and new treatment plans along with different substitutes of antimicrobial therapies (Jamal, 2023). Antibiotic resistance is an emerging issue that can be prevented by developing methods which is a worldwide task in both sectors of life sciences and public health. Over the past few decades, human-pathogenic microorganisms which show antibiotic resistance have risen globally. Many of the infections caused by these microbes can't be treated through traditional therapies, and even last-resort antibiotics are no longer effective. Furthermore, no new antibiotics have been discovered at an industrial level. In regard of World Health Day, there is an increase in research activity which was held by WHO under the theme "Combat drug resistance: no action today means no cure tomorrow." There is development of various promising strategies that help in restoring new treatment options in response to the disease and conditions caused by these resistant kinds of bacterial pathogens (Murugaiyan et al., 2022).

Many concerns regarding public health have risen due to the emerging trends in the spreading of antibiotic resistance in pathogenic microorganisms, in recent decades. It has been observed that the resistome, a reservoir of ARGs, can be transferred via HGT (horizontal gene transfer) by these pathogenic microbes are helps to acquire resistance. Resistome doesn't contain only ARGs which are present in clinical pathogens, but it contains that of all commensal, pathogenic, and environmental bacteria, as well as also the bacteriophages and mobile genetic elements (Barik et al., 2025). So, it's shown that ARGs can be transferred via HGT from environmental and commensal microorganisms to pathogenic ones to extravagate antibiotic resistance spread. To control this spread one should understand the concept of resistome and the process via which it can move into pathogenic bacteria. Various mechanisms of HGT play roles in the transmission of resistance against antibiotics and there is HGT of clinically important ARGs (Barik et al., 2025). In recent decades, there has been an alarming rise in the number of multidrug-resistant bacteria, which can lead to major issues. As the rise in resistant-related infections causes an increase in morbidity and mortality rates so, it's the need of an hour to discover new ways to deal with bacterial resistance (Chinemerem Nwobodo et al., 2022). There are some mechanisms described in Figure1 through which resistance is produced in bacteria.

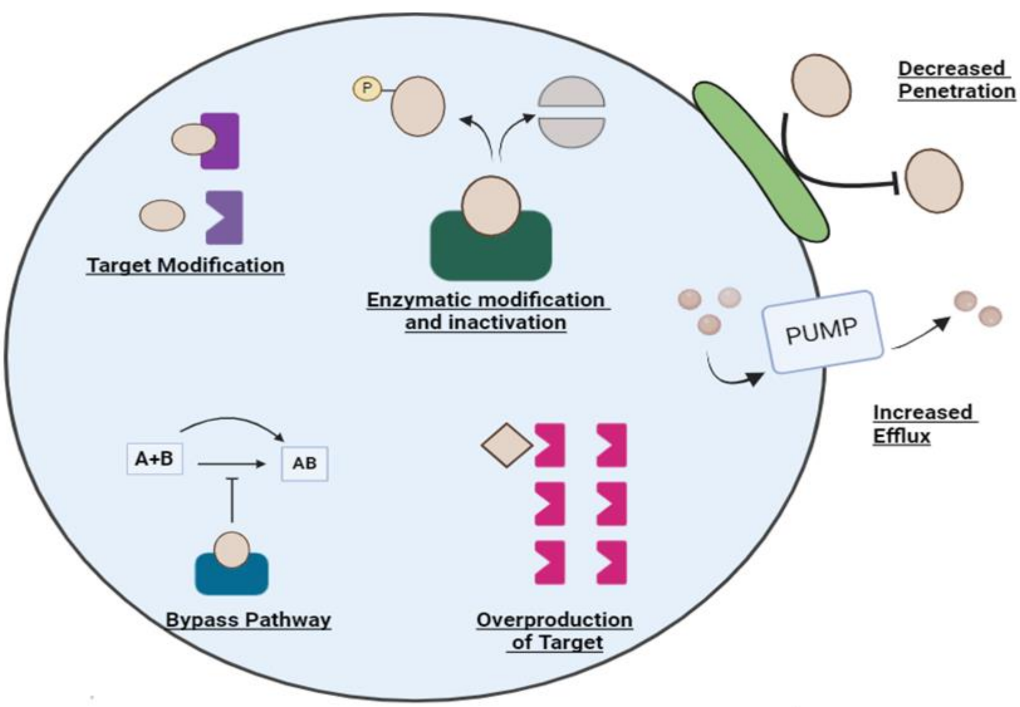

Fig. 1: Different mechanisms of bacteria to become resistant to antibiotics (Retrieved from BioRender)

Probiotics

"Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" are the probiotics (Das et al., 2022). The two most prevalent probiotic groups are lactobacilli and bifidobacteria; however, probiotics from other genera, including *Saccharomyces cerevisiae var. boulardii*, *Escherichia coli*, and *Bacillus coagulans*, are also sold commercially. Additionally, "new" species of probiotic-producing bacteria, such as *Faecalibacterium prausnitzii*, *Eubacterium halii*, and *Akkermansia muciniphila*, have been discovered and are being studied for their potential as probiotics shown in Table 1 (Das et al., 2022). Probiotics can improve your health in several ways, including your immune system, metabolism, digestion, and even your mental state. There is a general understanding that health advantages are specific to strain and can't be assumed for other strains, not even to the one belon g to the same species (Puvanasundram et al., 2021).

Table 1: Potential Probiotics used as an alternative to Antibiotics

Probiotic	Mechanism of action	References
Lactobacilli	• Competitive exclusion • Antimicrobial production • Strengthen the intestinal barrier • Short-chain fatty acid (SCFA) production	(Šola et al., 2022)
Bifidobacteria	• Modulating the immune system • Preventing pathogen adhesion • Bacteriocin production • Metabolizing aromatic amino acids	(Šola et al., 2022)
S. cerevisiae var. boulardii	• Bind and neutralize pathogens • Anti-inflammatory • Boost immune system	(Das et al., 2022)
E. coli	• Microcin production • Competitive exclusion • Reinforcing the intestinal barrier	(Das et al., 2022)
B. coagulans	• Production of anti-inflammatory cytokines • Bacteriocin production	(Šola et al., 2022)
F. prausnitzii	• Maintain gut barrier • Epigenetic regulation for anti-inflammatory effects	(Das et al., 2022)
E. halii	• Support gut barrier function • SCFA production • Maintain intestinal metabolic balance	(Puvanasundram et al., 2021)
A. muciniphila	• Reduce levels of pro-inflammatory cytokines • SCFA production • Interacts with the gut-brain axis (impact neuropsychiatric conditions)	(Puvanasundram et al., 2021)

Antibiotics and probiotics can be used together to prevent the emergence of drug resistance. Probiotics can also lessen overall drug dependence by counteracting several antibiotic adverse effects, including discomfort, inflammation, and electrolyte imbalance brought on by disruptions in the gut microbiota (Elshaghabee and Rokana, 2022). Many randomized controlled trials elaborated the positive aspects of probiotics use in the treatment of AAD, it includes experiments by using the specific strains that employ *Saccharomyces* and *Lactobacillus* as well as meta-analyses (Kopacz and Phadtare, 2022). Bacteriocins and probiotics used in dairy animals can help to reduce antimicrobial resistance. This shows that probiotics can show their activity by using mechanisms like production of bacteriostatic and other growth inhibitory components like H_2O_2 organic acids and bactericidal components i.e. bacteriocins (Monika et al., 2021).

Probiotics' Antibiotic Resistance Profile

Concerns have been raised, and business groups and regulatory bodies have started to offer advice on how to evaluate the risk of antibiotic resistance transmission via probiotics (Zavišić et al., 2023). As in probiotics, acquired genes can be transmitted via transposases, prophage/bacteriophage elements and conjugative plasmids so it raises the safety concerns which need to be focused (Anadón et al., 2021). Most isolates from commercially available brands of probiotic preparations containing *Lactobacillus* were susceptible to carbapenems (imipenem, meropenem, and ertapenem), penicillin-type (ampicillin and amoxicillin) antibiotics, and inhibitors of protein synthesis (clarithromycin, chloramphenicol, linezolid, erythromycin, and tetracycline) but resistant to vancomycin. And the *tet*K gene for tetracycline resistance is also present. As a result, lactic acid bacteria are resistant to several antibiotic types, such as macrolides, β-lactams, and aminoglycosides (Selvin et al., 2020). Metronidazole resistance is also an added advantage to *Lactobacillus* in case of *C. difficile* infection, as it is one of the choices for its treatment (Das et al., 2020).

Risk of Antibiotic Resistance Spread with Probiotics

We can gain the resistance genes from the bacteria we ingested and then they are stored in colonic bacteria. As different mechanisms are involved in the incidence of antibiotic resistance, one of them is horizontal gene transfer of the plasmids (or other mobile genetic elements) which extravagate the AMR spread within microorganisms. HGT is more common in the human GIT between intestinal microbiome, pathogenic microorganisms and probiotic's microorganisms (both yeast and bacteria) (Daniali et al., 2020). Members of the genera Streptococcus, Enterococcus, and some other lactic acid bacteria (LAB) contain some opportunistic pathogens, but members of the genera *Lactobacillus* and Lactococcus are most frequently designated as "generally regarded as safe" (GRAS) or Qualified Presumption of Safety (QPS) (Mourenza et al., 2020).

Numerous studies have examined the use of enterococcal species as probiotics due to their good probiotic qualities, such as their resistance to bile salts and gastric juice, their stability during handling and storage, and their production of enterocin (a bacteriocin) (Darbandi et al., 2022). Antibiotic resistance genes to numerous therapeutically significant antibiotics encoded on a broad range of conjugative plasmids, transposons, and bacteriophages are easily acquired by *Enterococci*. *Enterococci* are not good probiotics because of their toxicity and disease burden. However, several virulence traits, such as cytolysin, proteases, aggregation substance, capsular polysaccharide, enterococcal surface protein, biofilm formation, intestinal translocation, extracellular superoxide, and resistance to innate immunity, are expressed by this microorganism and can result in serious hospital-acquired infections (Wang et al., 2020). *Enterococci* have the potential to transfer AMR genes from the environment to people, and the danger is increased by their ability to spread those genes to the host microbiome through horizontal gene transfer (Cattoir, 2022).

Benefits of Probiotics

Probiotics are live microorganisms that improve the intestinal microbiota and offer health benefits to a host when consumed in sufficient quantities (Binda et al., 2020). These bacteria create antimicrobial peptides called bacteriocins, which alter the composition of the gut microbiota in animal models including mice, pigs, and chickens and typically inhibit or kill pathogenic bacteria in the gut (Anjana and Tiwari, 2022). Through competition, niche clearing, and spatial segregation, probiotic bacteria that produce bacteriocin that colonize the gut prevent pathogens from adhering to intestinal epithelial cells (Heilbronner et al., 2021).

Probiotics may help prevent drug-resistant infections in people, but this is still up for debate. The Centers for Disease Control and Prevention (CDC) are conducting extensive research on the topic; nevertheless, while some studies have demonstrated benefits, the information is still insufficiently clear to make firm recommendations currently (Merenstein et al., 2024). Probiotics can now be used to treat multidrug-resistant UTIs by either partially replacing or supplementing antibiotic therapy. Most of the studies on antibiotic resistance have been on pathogenic bacteria that are common in nosocomial environments, such as hospitals and nursing homes. Antibiotic resistance is a much bigger issue, and research on antibiotic resistance in aquaculture and food animal production is also important (Zhao et al., 2021).

Since mobile genetic elements frequently carry antibiotic-resistant genes, it's critical to understand how these elements circulate throughout the food chain. Antibiotic growth promoters (AGPs) are still in use around the world despite being outlawed in Europe in 2006 (Kalia et al., 2022). Furthermore, veterinary care in Europe continues to make extensive use of antibiotics to treat disease in producing animals. To lessen the selection pressure on the emergence, evolution, and dissemination of antibiotic resistance, we must better understand the ecology of resistance. This calls for more focused treatments. The use of probiotics in feed has the potential to improve animal health and slow the emergence of antibiotic resistance.

Conclusion

Probiotics have been shown to have numerous advantageous impacts, including reductions in antibiotic use, which is one of the best-documented benefits of probiotics. The majority of these advantages are related to AAD, but they also include maintenance of the composition as well as the function of the intestinal and other bacteria. Antibiotic resistance should not spread as quickly or evolve as a result of this. To have a better knowledge of the opportunities, future probiotic studies examining the influence on antibiotic use should search for the existence or absence of relevant resistance genes. Since the tools and the chances are there, it is important to give it greater attention because, from a global standpoint, minimizing resistance spread might be more advantageous than reducing AAD.

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