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## ANTIBIOTIC RESISTANCE IN LACTIC ACID BACTERIA: A REVIEW

KUMAR D<sup>1</sup>, UPADHAYAY D<sup>2</sup>, MARCHAWALA F<sup>2</sup>, BHATTACHARYA I<sup>2</sup> AND  
ANDHARE P<sup>2\*</sup>

1: Student, MSc Microbiology, Parul Institute of Applied Sciences, Parul University, Post  
Limda, Waghodia, Gujarat, 391760

2: Assistant Professor, Parul Institute of Applied Sciences, Parul University, Post Limda,  
Waghodia, Gujarat, 391760

\*Corresponding Author: E Mail: Dr. Prasad Andhare: [prasad.andhare82145@paruluniversity.ac.in](mailto:prasad.andhare82145@paruluniversity.ac.in); Tel:  
+918200614350

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### ABSTRACT

Probiotics are live microorganisms that offer the host a health advantage when administered in appropriate quantities. The key probiotic bacteria are strains belonging to the *Lactobacillus* and *Bifidobacterium* genera, although other agents have also been used, such as strains of *Bacillus* or *Escherichia coli*. Two famous inhabitants of the human intestinal microbiota are *Lactobacillus* and *Bifidobacterium*. In food fermentation processes, some organisms are often used as starters or as adjunct crops in the food industry. With certain cases, where mutations or intrinsic resistance mechanisms are responsible for the resistance phenotype, antibiotic resistance in these beneficial microbes does not constitute a safety issue in itself. In fact, after antibiotic treatment, some probiotic strains with intrinsic antibiotic resistance may be useful for restoring the gut microbiota. However, in the traditional probiotic genera, unique antibiotic resistance determinants carried on mobile genetic elements, such as tetracycline resistance genes, are frequently identified and constitute a resistance reservoir for potential food or gut pathogens, thus posing a serious safety problem.

**Keywords:** Antibiotics, bacteria, LAB, *Lactobacillus*

## INTRODUCTION

One of the three greatest threats to human health has been described as antibiotic resistance [1]. High medical costs, increased cases of hospitalization, and mortality rates are correlated with the global spread of bacterial antibiotic resistance. It is estimated that at least 2 million individuals in the United States are infected with antibiotic-resistant bacteria annually, with over 23,000 deaths as a result [2]. There is therefore a demanding need to control the spread and reduce the risk of antibiotic resistant bacteria in various industries, such as agri-food. As a consequence of inherent structural or functional characteristics, bacteria can be intrinsically resistant to antibiotics, but can also acquire antibiotic resistance through chromosomal gene mutation or exogenous DNA acquisition. There is a limited horizontal propagation capacity for intrinsic resistance and resistance due to chromosomal mutation, while resistance can be more easily disseminated due to the acquisition of mobile genetic elements (e.g., plasmids or transposons) [3].

Antimicrobial resistance has become one of humanity's primary safety concerns, and a number of organizations, including the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the US

Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), have raised awareness of the issue. Antimicrobial resistance can occur when microorganisms (bacteria, fungi, viruses and parasites) are continuously exposed to antimicrobials (antibiotics, antivirals, antifungals, etc.) and some microorganisms can survive and develop in the presence of antimicrobials as a result of the adaptation process, which would inactivate them under normal circumstances [4]. In particular, antibiotics are drugs used to treat human and animal bacterial infections, to prevent or inactivate the reproduction of bacteria through several mechanisms, either to inhibit cell wall or cytoplasmic membrane synthesis, to block protein synthesis or to copy DNA processes, altering the metabolism, or acting directly against the bacterial resistance pathway [5]. From 2000 to 2010, the use of human antibiotics (cephalosporins, broad-spectrum penicillin and fluoroquinolones) increased by 36%, mainly because of their inappropriate prescription and consumption for the treatment of viral rather than bacterial infections. This fact can be correlated with the global antimicrobial resistance report that points to more than 700,000 antimicrobial resistance-related human deaths each year,

with a scenario increasing to 10 million death [6].

The growing world population is leading to increased food demand, where antimicrobials such as antibiotics and fungicides are commonly used to treat infections in food-producing animals (cattle, pigs, poultry and fish), as well as in crops, to prevent diseases and to promote development. In developing countries where unregulated large quantities of antibiotics are used that have been associated with the incidence of multiple antibiotic-resistant strains of *Enterococcus* and *Lactobacillus* from Indian poultry, this practice is also seen [7]. The FAO also estimates that 90% of antibiotics can be excreted in water and soil, thus contaminating the environment, resulting in increased exposure and production of AR microorganisms that can transfer their resistant genes to other microorganisms for example, animals exposed to antibiotics (tetracycline, penicillin, sulphonamide, and polymyxins) were five times more likely to be immune to bacterial communities in the intestine [8]. Resistant microorganisms may be transmitted from infected food and water or from the atmosphere to humans (FAO 2017). In combination with good hygiene and husbandry practices, various procedures such as adequate animal vaccination and the use of

additives that promote health and feed conversion efficiency will minimize the need for antimicrobials and antibiotics for food production.

#### **ANTIBIOTIC RESISTANCE TYPES:**

Antibiotics were introduced for the treatment of microbial diseases around 50 years ago. Since then, the growth of antimicrobial resistance in pathogenic bacteria has been the biggest obstacle to the use of antimicrobial agents for the treatment of bacterial infections. The rate of development of antimicrobial resistance is predicted to be increased by the misuse of antibacterial substances, according to the World Health Organization (WHO) Global Strategy for the Containment of Antimicrobial Resistance. Three kinds of resistance exist: natural (intrinsic or inherent), acquired and mutational. For an antibiotic to be successful against bacteria, three requirements must be met: (i) there must be a susceptible antibiotic target in the cell, (ii) the antibiotic must meet the target in adequate amounts, and (iii) the antibiotic must not be inactivated or changed. Five main modes of antibiotic activity pathways exist:

1. Interference with cell wall synthesis
2. Inhibition of protein synthesis
3. Interference with nucleic acid synthesis.
4. Inhibition of a metabolic pathway

## 5. Disorganizing of the cell membrane

### LACTIC ACID BACTERIA:

The term lactic acid bacteria refer to a taxonomically diverse group of Gram-positive, optional anaerobic, non-forming, non-motile, and acid-tolerant cocci, coccobacilli, or rods with common metabolism and physiology capable of fermenting sugars primarily into lactic acid, appearing as single cells or forming couples, tetrads, or long chains (Álvarez-Cisneros & Ponce-Alquicira, 2018)[9]. Two phyla, the Firmicutes and the Actinobacteria are found in LAB species; *Aerococcus*, *Alloiococcus*, *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus*, and *Weissella* belong to the Bacilli class and the *Lactobacillales* order for the first genus, which are low G + C (31-49 percent). The Actinobacteria phylum belongs to the genus *Bifidobacterium* with a high G + C content (58-61 percent) [10].

LAB is anaerobic, but, unlike most anaerobes, they grow as aerotolerant anaerobes in the presence of O<sub>2</sub>. Although many genera of bacteria produce lactic acid as a primary or secondary fermentation end product, in addition to *Carnobacterium*, *Enterococcus*, *Oenococcus*, *Tetragenococcus*, *Vagococcus*, and *Weissella*, the term Lactic

Acid Bacteria is conventionally reserved for genera in the order *Lactobacillales*, which includes *Lactobacillus*, *Leuconostoc*, *Pediococcus*, *Lactococcus* and *Streptococcus*. Other genera include: *Aerococcus*, *Propionibacterium*, *Microbacterium*, and *Bifidobacterium* [11]. Some of the most important groups of microorganisms used in food fermentation are lactic acid bacteria. The use of different strains of LAB as probiotics has been of much recent interest because these bacteria, mainly lactobacilli and *bifidobacteria*, may have several therapeutic functions. Probiotics are defined as viable microorganisms that, by improving their intestinal microbial balance, exhibit a beneficial effect on the health of the host. *Bifidobacterium* spp. and *Lactobacillus*. Prominent members of the commensal intestinal flora are prominent. They cause decreased lactose sensitivity, reduced diarrhoea, decreased blood cholesterol, improved immune response, and cancer prevention. In the lactic acid bacteria used as probiotics are given [12].

According to the end products derived from glucose metabolism, this bacterial group is categorized into homofermentative and heterofermentative. The homofermentative transforms glucose mainly through the Embden-Meyerhof pathway into lactic acid,

while the heterofermentative LAB transforms glucose through the 6-phosphogluconate pathway into lactic acid, carbon dioxide and ethanol or acetic acid [13]. Because of their great acid tolerance and ability to adapt to redox changes, LAB are able to inhibit the growth of spoilage and pathogenic bacteria based on nutrient and adhesion niche competition. In addition, LAB is capable of developing antimicrobial metabolites such as lactic and acetic acids, ethanol, hydrogen peroxide, diacetyl, antimicrobials (short-chain fatty acids derived from lipolysis reactions), bacteriocin-like antimicrobial peptides and other antibacterial proteins such as peptidoglycan hydrolases (PGH) capable of breaking the Gram-+ve and Gram -ve bacteria peptidoglycan cell wall [14]. By forming pores in the cytoplasmic membrane, bacteriocins are ribosomal antimicrobial peptides active against closely related and unrelated responsive bacterial strains and responsible for reducing microbial LAB competitors under stress conditions. Several studies have shown the ability of bacteriocins for their action against spoilage microorganisms and pathogens such as *Listeria monocytogenes* and *Staphylococcus aureus* to be used for food preservation and in the pharmaceutical industry.

#### **ANTIBIOTIC RESISTANCE IN LACTIC ACID BACTERIA:**

Commonly used as probiotics or in starter cultures, lactic acid bacteria may serve as a host of genes for antibiotic resistance with the possibility of gene transfer in many lactic acid bacteria and other pathogenic bacteria [15]. Several methods have been applied to evaluating the efficacy of probiotics. The assessment of probiotic protection starts with the proper identification of the strain. In the safety evaluation of probiotics, laboratory studies include in vitro assays evaluating the various intrinsic properties of strains, such as resistance to antibiotics or the development of toxic metabolites, and different animal models that can be used to evaluate the ability of probiotics to translocate bloodstream and tissues from the intestines of the hosts to the hosts or assess the infectivity of the probiotics in different disease model [16]. Furthermore, in clinical trials, the efficacy of probiotics can be tested. Determination of antibiotic resistance properties is one of the key goals of in vitro safety assessments of current and potential probiotic strains. Resistance to a certain antibiotic by a probiotic strain is clinically important only in the case of infections, and infections related to probiotics are extremely rare [17] considered it is necessary, however,

to carry of genes of antibiotic resistance that can be horizontally transferred to other microorganisms, whether pathogenic or present in the gastrointestinal microbiota, which can trigger a health problem due to continuous exposure to environmental conditions that favour the spread of resistance that threatens the public health and the food production. The collection of probiotic strains free of transferable antibiotic-resistance determinants should be given continuous attention. The unregulated use of antimicrobial agents in agricultural practice has certainly assisted the spread of resistant species. It is therefore important to have much tighter control over the use of these medications.

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