

# LACTOBACILLUS AS A RESERVOIR OF ANTIBIOTIC RESISTANCE GENES

## Abstract

Fermented dairy products have been used since ancient times for their nutritional and probiotic properties, earning them a central place in diets around the world. However, the uncontrolled use of antimicrobial drugs in veterinary medicine and the food industry has introduced a paradox in their beneficial role. These products, while known for their positive impacts, also have the potential to harbor antibiotic-resistant (AbR) genes and bacteria. An in-depth analysis of the effects of antibiotic-resistant bacteria and genes in fermented foods reveals potential serious consequences for human health, the food industry, and animal health alike. The presence of antimicrobial residues in dairy products exerts negative pressure on their microbial flora, potentially resulting in the amplification of antimicrobial resistance genes. This chapter delves into the abundance of data regarding antibiotic resistance in fermented dairy products, with a particular emphasis on antibiotic resistance in *Lactobacillus* species. Additionally, it sheds light on the potential transferability of antibiotic resistance genes to both pathogenic and non-pathogenic strains in the human gut. The comprehensive discussion provided here addresses the presence of various antimicrobial resistance genes within *Lactobacillus* and the potential for their transfer to various bacterial strains.

**Keywords:** Lactobacillus, bacteria, genes, drugs.

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## I. INTRODUCTION

The practice of fermentation has ancient roots and has been employed for various food products to extend their shelf life, enhance their organoleptic properties, and provide numerous health benefits. Among these fermented foods, dairy products hold a special position due to their probiotic attributes, which contribute to maintaining gut flora and bolstering the immune system. Across the globe, these products have secured a distinctive place in diets, thanks to their ability to confer unique flavors, tastes, and textures, owing to the diverse and complex bacterial flora they host.

The metabolic activities of microflora play a pivotal role in breaking down intricate compounds into more easily digestible ones. This process not only imparts specific essences and textures to the food but also elevates the nutritional qualities of the end products. However, these attributes are contingent upon factors such as the type of microflora present, fermentation duration, pH levels, and other handling specifics. The microbiological composition of food products can either originate from the environment, being naturally present in raw materials, or be intentionally introduced as starter cultures.

In the context of traditionally fermented milk and meat products, reliance is placed on the indigenous natural flora present in the raw materials. This practice often leads to the species profile of these products reflecting their local environments. An illustrative study comparing *Lactobacillus paracasei* strains from diverse Italian food products demonstrates distinct strains associated with each product. Conversely, industrial processes harness various bacterial strains to achieve desired flavors, textures, and nutritional qualities.

A dominant player in both traditionally prepared and commercial fermented products is the group of lactic acid bacteria (LAB). Despite the emphasis on proper hygiene, raw milk and meat remain reservoirs of environmental LAB. These environmental lactobacilli species, characterized by probiotic attributes, withstand food processing, proliferate during fermentation, and constitute a substantial portion of dairy products. Upon consumption, they traverse the human gastrointestinal tract, where interactions between the rich gut microbiome and the indigenous flora of fermented foods trigger a cascade of genetic material exchanges.

## II. MICROBIAL PROFILE OF FERMENTED FOOD PRODUCTS

Fermented foods stand as a testament to the prevalence of lactic acid bacteria (LAB), a substantial group encompassing gram-positive bacilli/cocci. These microorganisms exhibit characteristics like catalase negativity, non-spore formation, and the ability to ferment sugars into lactic acid, whether through homo- or hetero-fermentation. This bacterial cohort also produces valuable metabolic by-products, including lactic acid, organic acids, peptides, and hydrogen peroxide. Such compounds not only enhance food shelf life but also deter the proliferation of pathogenic and spoilage microorganisms.

A medley of genera within the lactic acid bacteria family, including *Lactobacillus*, *Pediococcus*, *Enterococcus*, *Leuconostoc*, and *Lactococcus*, play pivotal roles in the food and beverage industry. However, their influence isn't confined to consumables; these bacteria also inhabit the gastrointestinal and urogenital tracts of both animals and humans. Their prevalence within the human intestinal flora is particularly noteworthy, with genetic

similarities of approximately 65%-75% observed between dairy and commensal strains, underscoring subtle genetic differentiations.

The presence of lactic acid bacteria in animal feed garners attention for the benefits they bestow. These range from bolstering the health of young animals through inhibition of pathogenic species to fostering improved lactose tolerance, heightened immune responses, and the suppression of pathogenic microbes in humans.

However, despite the numerous advantages they offer, these microbial interactions can potentially catalyze genetic evolution within the gut microbiome. Intriguingly, a study on avid sushi consumers unveiled a resident gut bacterium harboring genetic material from marine bacterial species. If these genetic adaptations bolster the bacterium's ability to endure adverse conditions, it could lead to their proliferation. A pertinent example involves the acquisition of antibiotic resistance genes, enabling survival in the presence of antimicrobial agents.

The critical examination of the microbial composition in fermented foods is pivotal to ensuring food safety. Recent research has illuminated the presence of antimicrobial resistance in lactic acid bacteria within fermented dairy products. The factors behind this phenomenon may include the undue use of antimicrobial drugs or stressors encountered during the fermentation process. Remarkably, these bacteria navigate a range of stressors during fermentation, encompassing high salt concentrations, low pH levels, and the presence of antimicrobials. While some bacteria surmount these challenges through intrinsic mechanisms, others acquire survival traits via horizontal gene transfer. This dynamic has potential repercussions when food products harboring antibiotic resistance genes intersect with gut commensals, potentially disseminating these genes and limiting treatment options for bacterial infections.

### **III. ANTIMICROBIALS IN DAIRY ANIMALS**

The utilization of antimicrobials in dairy animals plays a multifaceted role in safeguarding animal health and ensuring food safety. As essential tools in modern livestock management, antimicrobials aid in preventing and treating infectious diseases among dairy cattle, thereby supporting overall herd well-being and productivity. Antimicrobials are judiciously employed to address a range of health concerns, including bacterial infections, mastitis, respiratory ailments, and other diseases that can compromise animal welfare and milk quality. Strategic administration of antimicrobials aids in curbing the spread of infections, minimizing suffering, and preserving milk yield. Yet, the prudent use of these agents is pivotal to mitigating the emergence of antimicrobial resistance (AMR), a global concern impacting both animal and human health.

Antibiotics have played a pivotal role for decades in preventing and treating various infectious diseases in animals. The collaborative report from the European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), and European Medicines Agency (EMA) underscored that antibiotic usage in food-producing animals surpassed human consumption between 2016 and 2018. Disturbingly, projections by Tiseo et al. predict an alarming 11.5% surge in antibiotic usage by 2030.

Preventing mastitis, a prevailing infection among dairy animals, drives substantial antimicrobial use. In the United States, nearly every dairy cow receives intra-mammary prophylactic doses for future mastitis control, with approximately 16% of cows receiving antibiotics for mastitis during lactation. Worryingly, escalated antibiotic use in significant diseases like respiratory and uterine infections, as well as its uptick in dairy sheep and goats, marks a mounting concern. The unregulated administration of antibiotics in veterinary medicine exerts selective pressure on bacterial strains, driving the amplification of individual bacterial resistant genes.

Unfortunately, inadequate consideration of drug withdrawal periods by veterinarians and dairy owners leads to antibiotic residues lingering in dairy products. Although most drugs undergo metabolism and elimination via urine or feces, some drug metabolites accumulate in liver, kidney, and, to a lesser extent, the site of administration. A comprehensive analysis of 73 scientific studies spanning 1999 to 2019 confirms the presence of antibiotic residues in animal-derived food products (16). Notably, beta-lactam antibiotics manifest higher concentrations in whey, a cheese byproduct, compared to the cheese itself (17). This concerns us even more when whey is recycled into subsequent food items.

Various strategies have been explored for eliminating antibiotic residues from food products, accompanied by a rigorous assessment of their effects. For instance, thermal treatment's efficacy in milk, particularly during yogurt and cheese production, is limited in degrading antibiotic residues. The concentration discrepancy between antimicrobial residues in yogurt and raw milk is marginal. Not only do these residues exert negative pressures on bacterial strains, potentially amplifying antibiotic resistance genes, but exposure to a single drug can also spur resistance to other drugs within the same class. Concurrently, instances of resistance to unrelated multiple drugs have been documented, often attributed to horizontal gene transfer, the predominant mechanism responsible for this pattern.

It is essential to navigate a delicate balance between reaping the benefits of antimicrobials and averting the potential risks they pose. Overuse or misuse of these agents can foster the development of resistant bacterial strains within the animal population, culminating in reduced treatment efficacy and the spread of resistant genes to humans through the food chain.

Antimicrobial stewardship, encompassing responsible prescription, accurate dosing, and proper administration, is pivotal to curbing AMR. Regulatory frameworks and guidelines are in place to guide veterinarians and farmers in employing these agents judiciously. Strategies such as disease prevention through vaccination, improved husbandry practices, and biosecurity measures are essential complements to minimize the need for antimicrobial intervention.

Addressing AMR necessitates a comprehensive, One Health approach, recognizing the interconnectedness of human, animal, and environmental health. Research into novel therapies, alternatives to antimicrobials, and innovative herd management practices is underway to secure the sustainability of dairy production while safeguarding public health.

#### **IV. ANTIMICROBIAL RESISTANCE (AR) IN LACTIC ACID BACTERIA**

The realm of antimicrobial resistance (AR) within lactic acid bacteria unveils the remarkable genome plasticity that empowers these microorganisms to exchange genetic material across diverse genera and species. This phenomenon underscores the dynamic nature of bacterial genomes and their capacity to disseminate resistance mechanisms.

Numerous reports have illuminated the interconnectedness of bacterial genetic landscapes, revealing a world where genes can traverse boundaries that once seemed insurmountable. The pliability of bacterial genomes, coupled with mechanisms like horizontal gene transfer, facilitates the sharing of genetic traits between different types of bacteria. This genetic promiscuity enables lactic acid bacteria, including prominent members like *Lactobacillus*, to partake in the dissemination of AR genes.

This ability to transfer AR genes between bacterial species amplifies the complexity of AR dynamics. Lactic acid bacteria, frequently associated with health-promoting attributes, can paradoxically harbor and transmit resistance genes. The coexistence of beneficial traits and the potential to perpetuate AR underscores the necessity of a comprehensive understanding of these mechanisms.

Bacterial genome plasticity serves as the bridge that connects the evolutionary history of bacteria with their contemporary interactions in various environments. This plasticity underpins the survival strategies of bacteria, enabling them to adapt swiftly to changes in their surroundings, including the presence of antimicrobial agents. As lactic acid bacteria engage in food production and inhabit diverse ecological niches, the potential for AR gene dissemination is particularly relevant.

As we navigate the landscape of AR in lactic acid bacteria, the role of genome plasticity cannot be underestimated. Vigilance in monitoring resistance patterns, understanding the mechanisms that facilitate gene transfer, and promoting responsible antibiotic use is crucial to curtailing the spread of AR within this group of bacteria. These efforts safeguard the integrity of fermented foods, the benefits of probiotics, and ultimately, human health.

In conclusion, the exploration of AR in lactic acid bacteria underscores the dynamic nature of bacterial genomes and their propensity to share genetic material across genera and species. This phenomenon sheds light on the intricate interplay between bacterial evolution, resistance mechanisms, and the challenges posed to human health and food systems.

#### **V. AMR IN LACTOBACILLUS**

The emergence and propagation of antimicrobial resistance (AMR) among bacteria, including beneficial species like *Lactobacillus*, pose a substantial challenge to both human health and the food industry. *Lactobacillus*, renowned for its contributions to fermented foods and probiotics, is now gaining attention as a potential reservoir and disseminator of AMR genes.

Traditionally perceived as innocuous, *Lactobacillus* species are increasingly found to harbor and transmit AMR genes. This phenomenon is of grave concern due to the widespread application of these bacteria in food production, where they influence flavor, texture, and nutritional quality. The intricate balance between the beneficial aspects of *Lactobacillus* and its potential to harbor resistance genes underscores the need for meticulous scrutiny.

The rise of AMR in *Lactobacillus* is attributed to various factors, including the misuse of antibiotics in agriculture and veterinary medicine. Antibiotic residues in animal feed, which can reach consumers through dairy products and other food items, contribute to the selection and propagation of resistant strains. Horizontal gene transfer, a mechanism enabling the swift spread of resistance genes between bacterial species, further compounds the problem.

*Lactobacillus*'s remarkable adaptability to diverse environments facilitates its survival amidst antibiotic exposure. These bacteria exhibit intrinsic resistance mechanisms, which, when coupled with acquired resistance genes, elevate their resilience. This adaptability extends to their coexistence with other gut microorganisms, potentially transferring AMR genes to pathogenic or commensal bacteria.

The transfer of AMR genes from *Lactobacillus* to other bacteria within the gut ecosystem presents a tangible threat. This genetic exchange, although less frequent compared to pathogens, remains a cause for concern, as it could limit treatment options for infections. Furthermore, the persistence of *Lactobacillus* carrying resistance genes in the gut raises questions about their potential to serve as reservoirs for future resistance development.

Addressing AMR in *Lactobacillus* warrants a multidisciplinary approach, encompassing prudent use of antibiotics in agriculture, veterinary practices, and food production. Strategies to minimize the dissemination of resistance genes involve careful selection of antibiotic treatments, improved waste management, and surveillance of resistance patterns in *Lactobacillus* populations.

The extensive use of antimicrobials in livestock coupled with their persistent interaction with gut flora has triggered the selection of antimicrobial-resistant (AbR) strains within the commensal gut flora of treated animals. The identification of AbR strains within the food chain serves as a critical conduit for resistance transmission between the gut flora of humans and animals. It's noteworthy that antimicrobials used in both veterinary and human medicine belong to shared classes, encompassing Cephalosporins, aminoglycosides, tetracyclines, and glycopeptides. Consequently, exposure to a solitary drug has the potential to foster cross-resistance spanning the human-animal interface.

A comprehensive examination of veterinary probiotics administered to animals underscores the gravity of the situation. An alarming 97% of these products have been found to harbor at least one antimicrobial resistance gene, while 82% harbor two or more (10). This unequivocally underscores the looming risk of antimicrobial resistance transmission through animal-derived products.

Antibiotic resistance within lactic acid bacteria (LAB) found in dairy products has garnered significant attention in recent years. Research spanning Indonesian fermented foods

like dadih, tape ketan, and tempoyak demonstrated notable resistance within LAB to chloramphenicol and erythromycin. Similar findings emerged from lactic acid bacteria isolated from Chinese pickles, revealing considerable antibiotic resistance, albeit with the exception of tetracycline, penicillin, and clindamycin. Genotypic analysis unveiled the presence of antibiotic resistance genes (ARGs) like *ermB* and *tetM* in both plasmid and chromosomal DNA segments.

*Enterococcus*, recognized as an opportunistic pathogen in humans, exhibited a considerable percentage of resistance to vancomycin within Turkish white cheese. A wealth of scientific studies probing *Lactobacillus* strains in fermented foods has unveiled a significant reservoir of antibiotic resistance genes residing within their genomes.

In a nutshell, the intricate nexus between antimicrobial use in livestock and the proliferation of AbR strains underscores the paramount need for heightened vigilance. The prevalence of antibiotic resistance in lactic acid bacteria within dairy products and fermented foods demands immediate attention to mitigate the risks of resistance transmission between animals, food products, and human populations.

## VI. PHENOTYPIC AND GENOTYPIC INSIGHTS INTO ANTIMICROBIAL RESISTANCE (AMR)

Investigations into various lactic acid bacteria strains have unveiled intriguing patterns of phenotypic resistance. Notably, a study by Comunian et al. (2009) delved into 121 *L. paracasei* strains, revealing that regions with more intense antimicrobial practices exhibited higher frequencies of resistant strains in fermented meat and milk products. This observation was substantiated by phenotypic and genotypic characterizations, highlighting the presence of tetracycline resistance determinants *tet(M)*, *tet(W)*, and erythromycin resistance determinant *erm(B)*. Strikingly, *Lactobacilli* strains from traditionally pasteurized cheese exhibited sensitivity to these antibiotics (18).

Further insights emerged from the examination of 46 *Lactobacillus* strains isolated from Turkish dairy products, where resistance was recorded against vancomycin (58%), erythromycin (10.8%), gentamicin (28%), ciprofloxacin (26%), and tetracycline (4.3%) (19). A concerning prevalence of antibacterial resistance surfaced in *Lactobacilli* against tetracycline (68%), lincomycin (64.5%), enrofloxacin (65%) in turkeys, with 47% of *lactobacilli* isolates displaying resistance to ampicillin (20).

*Lactobacillus johnsonii* and *Lactobacillus zeae*, sourced from raw milk of goats, sheep, and cows, exhibited significant resistance to erythromycin, with around 64.5% of isolates displaying resistance to three classes of antimicrobial drugs (21). Among 33 *lactobacillus* isolates, 19 showcased resistance against vancomycin, 10 against ciprofloxacin, and one against tetracycline, with genotypic confirmation of the presence of *van(X)*, *van(E)*, *gyr(A)*, and *tet(M)* genes (23).

A spectrum of antimicrobial resistance genes (ARGs) has been cataloged across several *Lactobacillus* species, including *L. delbrueckii* (gene *poxtA*), *L. acidophilus* (gene *poxtA*), *L. kefirifaciens* (gene *poxtA*), *L. lactis* (gene *lmrD*), and *L. mesenteroides* (gene *APH(3')-IIb*), isolated from kefir and yogurt samples. Intriguingly, despite the constant use

of penicillins and cephalosporins in dairy cows, no beta-lactam ARGs were reported in this metagenomic analysis. Notably, mobile genetic element (MGE) analysis unearthed the coexistence of ARG *ImrD* with transposase within a proximity of 10 ORFs, possibly augmenting its transferability to pathogenic or non-pathogenic strains within the human gut (27).

The presence of the *PoxA* gene across Enterococci, *Pediococcus acidilactiti*, clinical isolates of *Staphylococcus aureus* (MRSA), cow milk, and animal wastewater suggests its selection due to the excessive use of phenicols and antiribosomal agents in veterinary medicine (25). The identification of the *APH(3')-IIb* gene in *L. mesenteroides* warrants further investigation, given its prior identification in *Pseudomonas aeruginosa* from clinical isolates, and the potential contribution of transposon-mediated mechanisms to its dissemination (28).

Collectively, these findings underscore the role of *Lactobacillus* as a substantial reservoir of ARGs, with the potential to serve as conduits for the transfer of these resistance determinants across diverse bacterial strains and species.

## VII. HORIZONTAL GENE TRANSFER AND ANTIMICROBIAL RESISTANCE (AMR) IN FERMENTED FOODS

The diverse microbial communities thriving in fermented foods orchestrate a symphony of horizontal gene transfer (HGT), bestowing not only extended shelf life and sensory attributes but also posing a potential avenue for the exchange of resistance genes. This intricate dance of genetic material holds significance in both the enhancement of food products and the potential dissemination of resistance genes.

The human gut, a dynamic arena of interaction between commensal flora and dietary components, emerges as a prime hotspot for the dispersion of antimicrobial resistance genes (ARGs) through HGT. Genetic mobile elements (GMEs) such as transposons and plasmids act as key agents in facilitating the spread of ARGs, not only vertically to offspring but also horizontally across different genera (22). The presence of ARGs like *tetM* and *sul1* within *Lactobacillus bulgaricus* isolated from fermented milk products, coupled with their association with GMEs like conjugative transposons and plasmids, accentuates the looming risk of their transmission to humans (29,30).

Experimental demonstrations of plasmid-mediated transfer of antibiotic resistance between strains of *L. curvatus* underscore the dynamic nature of resistance dissemination (31). Plasmid-mediated streptomycin and gentamicin resistance genes within *L. ramosus* and *L. plantarum* further highlight the potential for HGT within probiotics (32). Filter mating experiments have revealed the wide host range of transconjugants for plasmid *Plf-1*, carrying the erythromycin resistance gene in *L. plantarum* strain M345. This plasmid's transferability to an opportunistic pathogen, *Enterococcus faecalis*, within a gnotobiotic rat model mimicking the human intestine, adds to the growing evidence of the risk of ARG transmission from probiotics and fermented foods to the human gut biome (34, 35).

The dynamic relationship between antibiotic administration in animals and the surge in ARGs, coupled with the increased co-occurrence of MGEs and ARGs, substantiates the



notion that antimicrobial pressure fosters the mobility of resistance genes in animals (33). Investigations showcasing the transfer of *vanA* genes during early soybean meal production, followed by their conveyance through the digestive tract of pigs, underscore the potential dissemination of ARGs from food additives (38).

Collectively, the scientific landscape highlights *Lactobacillus* strains from fermented foods as potential repositories of ARGs with the capacity to bridge the gap between food products and human health. As we strive to understand and mitigate the risks associated with the spread of AMR, these findings underscore the need for vigilant monitoring, responsible antibiotic usage, and strategies to curtail the transfer of resistance genes within microbial communities.

## VIII. CONCLUSION

Fermented food products, once deemed safe under the banner of "Generally Regarded as Safe" (GRAS), have now emerged as unexpected reservoirs of antibiotic resistance genes (ARGs). Among the prominent actors in this arena, *Lactobacillus*, renowned for its probiotic properties, has taken center stage. This once-beneficial genus of lactic acid bacteria (LAB) has now been revealed as a major carrier of ARGs, found both on plasmid and chromosomal DNA.

The burgeoning crisis of antibiotic resistance arises from the uncontrolled utilization of antibiotics in livestock. The emergence of patterns of antibiotic resistance in these otherwise beneficial microbial communities sheds light on the potential ramifications of widespread antibiotic administration in farm animals. The consequences of this trend are reflected in the genetic makeup of *Lactobacillus* strains found in fermented foods.

To unveil the intricate mechanisms underpinning the presence of these ARGs, rigorous genotypic studies of *Lactobacillus* strains from diverse sources, including food products and related environments, are paramount. Only through such investigations can we gain a comprehensive understanding of the drivers and implications of ARG dissemination within microbial communities, thereby informing strategies for combatting the escalating challenge of antibiotic resistance.

As fermented foods transition from culinary delights to critical components of the antimicrobial resistance puzzle, it becomes increasingly urgent to address this issue. A concerted effort is required, encompassing responsible antibiotic usage in agriculture, enhanced surveillance, and a deeper comprehension of the intricate interactions that govern microbial communities. This multifaceted approach is not only essential for preserving the integrity of our food products but also for safeguarding human health against the encroaching threat of antibiotic resistance.

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