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Review article

Antibiotic resistance and the safety of probiotic microorganisms

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Abstract

Background and Aim. Antibiotic resistance is a global threat to health. One of the current safety concerns regarding probiotic microorganisms is their antibiotic resistance, which is often associated with mobile genetic elements. There are risks of horizontal gene transfer of antibiotic resistance genes from commercial probiotic microorganisms - used in biologics, food, and feed additives - to pathogens affecting humans and domestic animals.

Materials and Methods. In this work, the criteria for assessing the safety of probiotic microorganisms, as set by researchers and national regulatory bodies, are summarised. The safety criteria set out in the most well-known QPS and GRAS systems are analysed in detail. The

literature on the antibiotic resistance of probiotic microorganisms was analysed from the following aspects: intrinsic and acquired resistance; phenotypic and genotypic profiles; species- and strain-level differences, and the role of the ecological niche.

Results. This study presents the results of an analysis of the safety and antibiotic resistance of probiotic microorganisms employed as biopreparations in public health measures, veterinary medicine, and the food industry. Safety assessment relies on a comprehensive approach, including the genetic characteristics of probiotic strains. The priority of full-genome sequencing and bioinformatic analysis is emphasised, as these enable a detailed review of the probiotic microorganism genome for the presence of genes determining the synthesis of virulence factors, antibiotic resistance, bioamines, and others.

Conclusion. The review emphasizes the importance of assessing the safety and antibiotic resistance of strains of lactic acid bacteria. Whole-genome sequencing of the strain is considered a priority.

Keywords: probiotic microorganisms; antibiotic resistance; whole-genome sequencing; safety.

Introduction

In the last few decades, the improvement of the quality of life, development of all branches of both fundamental and applied sciences, and consumer demand for healthier products have become key factors in the development of new strategies in the formulation of food products, including the rediscovery of the beneficial roles of lactic acid bacteria (LAB) in improving food safety [1].

The aim of this review is to analyse and summarise the findings of recent research on the safety and antibiotic resistance of probiotic microorganisms. These organisms are widely used in human and veterinary medicine as food and feed additives, as well as in the production of fermented products. The review summarises the results of 47 publications.

The majority of the reviewed studies highlight the relevance of molecular genetic methods in the safety assessment of probiotic microorganisms. Particular emphasis is placed on the importance of whole-genome sequencing, as it enables accurate identification of probiotic strains and the detection of genes associated with virulence, antibiotic resistance, biogenic amine production, and other traits of interest. The main safety criteria for probiotic strains include molecular genetic identification and a well-documented history of safe use, as supported by scientific research.

We analysed published articles on the antibiotic resistance of probiotic microorganisms using the following comparative aspects: intrinsic and acquired resistance, phenotypic and genotypic profiles, dependence on the ecological niche, and strain- or species-specific features. This approach enabled us to demonstrate that probiotic microorganisms carrying acquired antibiotic resistance genes pose a significant risk due to the possibility of horizontal gene transfer to pathogenic organisms. Accordingly, the review highlights the importance of analysing the genotype of probiotic strains for the presence of mobile antibiotic resistance genes. The analysis reveals significant differences in antimicrobial resistance profiles depending on the species or strain, as well as on the ecological niche - for example, isolates from the intestinal microbiota that are used in probiotics and starter cultures.

Materials and Methods

Search Strategy and Selection Criteria

A literature search was conducted using online databases, including Google Scholar, PubMed, Web of Science, and Scopus. The search criteria included articles related to the safety and antibiotic resistance of probiotic microorganisms. A total of 55 publications were selected for analysis.

The key search terms included phenotypic and genotypic profiles, strain/species specificity of antibiotic resistance, and the safety of probiotic microorganisms. Exclusion criteria involved the elimination of publications in which the study subjects were not probiotic microorganisms or in which antibiotic resistance and safety were investigated in other taxonomic groups.

Article Review and Data Extraction

The selected publications were analysed with a focus on extracting data related to phenotypic and genotypic methods used to assess antibiotic resistance in probiotic microorganisms. Particular attention was given to information regarding the presence of mobile genetic elements, such as plasmids, transposons, and others elements, carrying antibiotic resistance genes.

When analysing publications on the safety of probiotic microorganisms, particular attention was paid to molecular genetic methods for species and strain identification, with a primary focus on whole-genome sequencing. Bioinformatic analysis of the sequenced genome enables the detection of mobile antibiotic resistance genes, virulence factors, genes involved in the production of pro-inflammatory biogenic amines, and other undesirable traits.

The results of the analysis concerning the safety criteria and antibiotic resistance of probiotic microorganisms are presented in this article.

Results and Discussion

1. The safety of probiotic microorganisms

Probiotic microorganisms - primarily *Lactobacillus, Lactococcus,* lactic acid *Streptococcus, Leuconostoc, Bacillus species*, and yeasts - are widely used as biologics. They have a long history of safe use, and many species are included in the QPS (Qualified Presumption of Safety) and GRAS (Generally Recognized As Safe) lists [2].

Regulatory frameworks for assessing the safety of probiotic microorganisms used in fermented food products, as well as in food and feed additives, have been developed in the USA, the European Union, Russia, China, Australia, Brazil, South Korea, Canada, India, Thailand, and other countries. Overall, the structure of national regulatory policies concerning the safety assessment of probiotic microorganisms is similar across different countries.

The most widely recognized systems are the QPS framework, used by the European Food Safety Authority (EFSA), and the GRAS designation, regulated by the United States Food and Drug

Administration. The fundamental criteria in both systems include molecular genetic identification of the strain, inclusion of the species or strain in the QPS or GRAS lists, a documented history of safe use, and the absence of virulence traits. The criteria also consider that probiotic microorganisms in food and feed additives and fermented products can be a reservoir of mobile antibiotic resistance genes that can be horizontally transferred to other microorganisms, including pathogens.

A summary of the probiotic safety testing paradigm is presented in Figure 1 [3, 4].

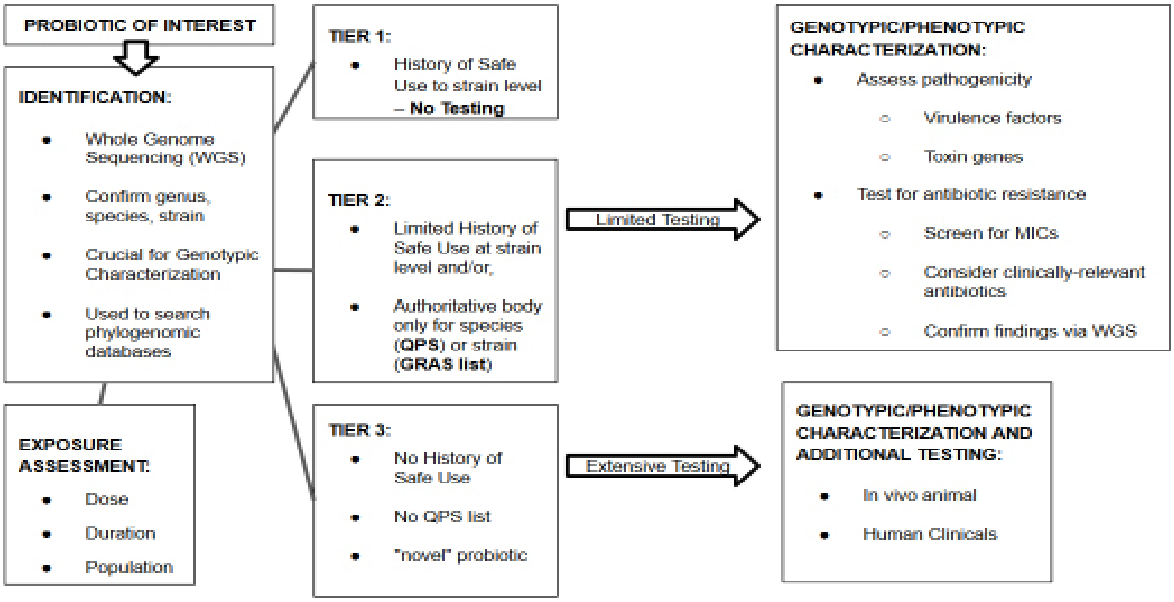

Figure 1. A proposed testing tier to guide data needs and studies for assessing probiotic safety

The safety assessment of probiotic microorganisms has significantly improved due to the increasing availability of whole-genome sequencing. This method is preferred because it enables a comparative analysis of detected undesirable genes - such as those responsible for virulence and antibiotic resistance - against genome databases of well - characterized probiotic strains/species listed in QPS or GRAS and used in commercial formulations.

The core internationally accepted safety criteria for probiotic microorganisms include molecular genetic identification of the strain/species and a well-documented history of safe use in probiotics, food and feed additives, and fermented products. The history of safe use must be substantiated by published scientific and methodological evidence.

If the strain's usage history is unclear or there are insufficient data, and the identified strain/species is not listed in GRAS or QPS, additional safety assessments are required, including in vivo studies using laboratory animals. Virulence and toxicity testing of probiotic microorganisms in animal models is essential during the development of new biologics, food products, or feed additives [3].

Our review of numerous published studies investigating the oral administration of probiotic microorganisms to laboratory animals did not reveal any evidence of virulent or toxigenic effects, regardless of the dose or duration of exposure. This calls into question the reliability of oral administration of live probiotic microorganisms to laboratory animals as a valid model for assessing human safety [4]. The classical method of oral administration of probiotic microorganisms in order to determine their virulent toxicity does not allow for the detection of certain negative characteristics of these microorganisms (hemolytic activity, production of pro-inflammatory bioamines, etc. Given the growing accessibility of whole - genome sequencing, there is increasing justification for its broad application as an *in vitro* tool for detecting toxicity - associated genes in probiotic strains.

Whole-genome sequencing is relevant not only for assessing the safety of probiotic strains but also for evaluating starter cultures [5]. A high-quality annotated genome sequence enables the identification of genes associated with antibiotic resistance, toxicity, as well as genes involved in the synthesis of exopolysaccharides and flavour-active peptides [6].

The necessity of investigating the safety of probiotic microorganisms arises from certain undesirable biological properties they may possess. For example, lactobacilli are capable of producing hydrolytic enzymes such as glycosidases, arylamidase proteases, and adhesive protein that bind to fibrinogen, collagen, and fibronectin, which can induce bacterial translocation within the host organism. Haemolysin, a protein toxin, has been described in strains of *Lacticaseibacillus rhamnosus (L. rhamnosus), Lacticaseibacillus zeae, Lacticaseibacillus saniviri* and et al. [7]. Moreover, lactic acid bacteria are known to produce decarboxylase enzymes that catalyse the synthesis of histamine, bradykinin, and other pro-inflammatory bioamines from amino acids [8]. Lactobacilli also have the ability to form biofilms and demonstrate enhanced adhesion to vascular endothelium, an ability attributed to the expression of genes responsible for exopolysaccharide and pili synthesis [9].

Given the growing use of probiotic microorganisms in human and veterinary medicine, as well as in food and feed additives, and the development of novel fermented products, ensuring the quality and safety assessment of these products is becoming increasingly important [6].

In Kazakhstan, the expanding development of probiotic and starter cultures for the fermentation of mare's milk and camel's milk [10, 11] underscores the relevance of using whole-genome sequencing as a core method for evaluating their safety.

2. Antibiotic resistance of probiotic microorganisms

1) Natural and acquired resistance

Resistance of probiotic microorganisms to antibiotics is categorised into natural and acquired resistance. Natural resistance can vary in antibiotic resistance profiles depending on the taxonomic affiliation and ecological niche of the organism. Natural resistance is typically stable and is not characterised by the possibility of horizontal transfer of resistance genes to other groups of microorganisms in the community. Natural resistance to antibiotics, determined by chromosomal genes, is considered an advantage of probiotic microorganisms, especially when used in conjunction with antimicrobials. Most lactobacilli show natural resistance to aminoglycosides (gentamicin, kanamycin, neomycin, and streptomycin), vancomycin, ciprofloxacin, and trimethoprim [12].

The natural resistance of lactic acid bacteria (LAB) to the glycopeptide antibiotic vancomycin, which disrupts peptidoglycan synthesis in the cells of Gram-positive bacteria, including penicillinase- and methicillin-resistant pathogens, is well known.

Resistance is due to the ability of LAB to alter the metabolic pathway of peptide synthesis by changing d-Ala-d-alanine to D-Ala–D-Lac or D-Ala–D-Ser, which reduce the affinity of vancomycin for the peptide precursor, thereby preventing vancomycin from binding to the microbial cell [13].

Phenotypic analysis of the resistance of 182 typical strains of lactobacilli isolated from different sources (human and animal intestines, inoculum, and fermented foods) to 16 antibiotics revealed the highest resistance to trimethoprim (152 of 182 strains, 84%), vancomycin (141 of 182, 77%), and kanamycin (111 of 181, 61%). These type strains were obtained from American, Belgian, Spanish, German, Japanese, Korean, and Spanish microbial collections. Genes encoding penicillin - binding proteins (PBP) and d -alanine -d -alanine ligase (Ddl), which determine resistance to vancomycin, have been identified in the genomes of lactobacilli [14].

Among the 15 tested strains of lactobacillus species (*L. plantarum, L. acidophilus, and L. pentosus*), *L. plantarum* strains were characterised by high antibiotic resistance [15]. The stable natural resistance of *L. plantarum* to vancomycin has been confirmed in recent studies [16].

A chromosomal mutation in a strain of *L. rhamnosus* was characterised by a specific mutation of the 23S rRNA gene, leading to a decrease in the affinity of erythromycin for microbial ribosomal proteins and thereby increasing the resistance to this macrolide antibiotic [17].

The antibiotic resistance profiles of 33 strains of lactobacilli isolated from fermented milk collected from various regions of China were studied. Antibiotic resistance was analysed by standard phenotypic methods and PCR analysis using gene-specific primers. Of 33 strains, 19 were resistant to vancomycin, 10 to ciprofloxacin, and one to tetracycline due to the presence of van(X), van(E), gyr(A), and tet(M) genes, respectively [18].

The resistance of lactobacilli to aminoglycoside antibiotics such as gentamicin, kanamycin, streptomycin, and neomycin has been described [19]. Resistance to aminoglycoside antibiotics has been attributed to the absence of cytochrome-mediated electron transport, a process necessary for the antibiotic to enter the microbial cell [20].

The known resistance of lactobacilli to fluoroquinolones (nalidixic acid, norfloxacin, moxifloxacin, gatifloxacin, and ciprofloxacin) is also due to natural resistance [21]. A study of lactobacilli isolates from commercial probiotic preparations and dietary supplements demonstrated resistance to amikacin, ciprofloxacin, and norfloxacin [22].

A review of published studies reporting antibiotic resistance in probiotic lactobacilli has shown that intrinsic resistance is more commonly observed against antimicrobial agents that inhibit the synthesis of microbial cell wall components [23].

Acquired antibiotic resistance, unlike intrinsic resistance associated with chromosomal determinants, is often mediated by mobile genetic elements (MGEs) such as plasmids and transposons. The localisation of antibiotic resistance genes on plasmids or transposons significantly increases the risk of horizontal gene transfer between different groups of microorganisms. Such horizontal transfer is most frequently facilitated by conjugative plasmids [24].

Although many probiotic microorganisms are recognised as being safe (GRAS) or included in the Qualified Presumption of Safety (QPS) list, molecular genetic studies have revealed that antibiotic resistance in probiotics is often mediated by MGEs. Lactic acid bacteria found in probiotics, fermented products, foods, and feed additives that carry mobile antibiotic resistance genes may transfer these genes to members of the intestinal microbiota after ingestion and colonisation of the gastrointestinal tract [25].

The active role of conjugative plasmids in the horizontal transfer of tetracycline resistance genes from *Lactiplantibacillus plantarum* to *Enterococcus faecalis* cells has been demonstrated in in vitro studies. The genes determining resistance to tetracycline - tet(M), tet(S), tet(W), tet(O), and tet(Q) - are known as the most frequently acquired resistance genes in lactobacilli [26]. At the same

time, an association of tet(M) with transposons was identified in Lactobacillus [14]. The mechanisms of action of the tet gene group include active efflux, ribosomal protection, and enzymatic modification of the antibiotic.

In a study conducted with another strain of *Lactiplantibacillus plantarum* that exhibited both phenotypic and genotypic resistance to tetracycline, no horizontal gene transfer was observed when the bacteria were co-cultivated with *Staphylococcus aureus, Listeria monocytogenes, Acinetobacter baumannii, Citrobacter freundii,* and *Escherichia coli*. The authors attributed the negative result to the fact that the tetracycline resistance genes in this Lactiplantibacillus plantarum strain were not associated with mobile genetic elements (MGEs) [27].

Probiotic microorganisms are often characterised by multiple antibiotic resistance. Thus, PCR analysis using specific primers for lactic acid bacteria strains from probiotic tablets has revealed the presence of genes involved in resistance to erythromycin, rifampicin, trimethoprim, chloramphenicol, quinupristin, vancomycin, and streptomycin. Multiple antibiotic resistance increases the risk of potential association with MGEs; therefore, studies aimed at determining the localisation of these genes are necessary to confirm or exclude their association with MGEs [28].

Experiments were conducted to evaluate the horizontal transfer of tetracycline resistance genes from lactobacilli to *Enterococcus faecalis, E. hirae, and Listeria* monocytogenes under different co-cultivation conditions: on nutrient media, in the intestines of laboratory animals, and as part of a fermented product. Regardless of the co - cultivation conditions, horizontal gene transfer occurred predominantly via conjugation [29-30]. A similar result was obtained in an earlier study when the tetracycline resistance gene tet (M), located on the transposon Tn916 in L. paracasei, was transferred to *E. faecalis* when they were co - cultured together [31].

An analytical review of 25 research studies containing the results of antibiotic resistance research demonstrated that nine reported positive findings on the horizontal transfer of antibiotic resistance genes from lactobacilli to pathogenic bacteria. Attention is drawn to the fact that horizontal transfer of tet resistance genes into lactobacilli cells increases the risk of the spread of antibiotic resistance, particularly among the elderly and newborns [23].

At the same time, studies on the antibiotic resistance of commercial probiotic microorganisms based on whole-genome sequencing have shown a low potential for horizontal gene transfer of antibiotic resistance determinants [32].

Strains of lactobacilli have also been described that contain mobile genetic elements (MGEs) - such as plasmids, transposons, and others - which encode the synthesis of acetyltransferases, nucleotidyltransferases, and phosphotransferases capable of neutralising the antimicrobial activity of aminoglycosides [33].

2) Phenotypic and genotypic profiles of antibiotic resistance. Probiotic microorganisms have been studied for resistance to the most clinically relevant antibiotics using both phenotypic and genotypic methods. For phenotypic assessment of antibiotic resistance in probiotic microorganisms, the E-test, the disk diffusion method, and the broth microdilution method to determine the minimum inhibitory concentration (MIC) of the antibiotic are employed. Among genotypic methods, PCR genotyping using gene-specific primers is the most frequently approach, and whole-genome sequencing is also considered an effective tactic.

Identifying antibiotic resistance by phenotypic methods does not determine the presence of resistance-determining genes within the microbial cell or their possible localisation in mobile genetic elements (MGEs). Conversely, even when phenotypic resistance is absent, the strain may harbor antibiotic resistance genes within MGEs [34]. Thus, the presence of antibiotic resistance genes in a microbial cell does not necessarily imply functionality, as they may be rendered inactive due to stop codons or mutations such as insertions or deletions. Therefore, it is recommended to combine phenotypic and genotypic analyses when assessing antibiotic resistance.

The following results of a comparative study on the phenotypic and genotypic resistance of probiotic microorganisms to antimicrobial agents are particularly illustrative. The researchers compared the phenotypic and genotypic resistance profiles of 182 *Lactobacillus* strains to 16 antibiotics belonging to the most important classes of antimicrobials used in human and veterinary medicine.

Among 79 *Lactobacillus* strains that exhibited phenotypic resistance to chloramphenicol, only 20 possessed the corresponding genetic determinants. Conversely, among 82 strains that showed phenotypic susceptibility to this antibiotic, 59 carried antibiotic resistance genes. Similarly discrepancies between phenotypic and genotypic antibiotic resistance were observed for tetracycline and erythromycin: resistance genes were detected in only 12.7% and 10.3%, respectively, of phenotypically resistant strains. Overall, among the 182 *Lactobacillus* strains examined, phenotypic resistance was correlated with the presence of corresponding resistance genes in 67% of cases.

The same study reported a high correlation between phenotypic and genotypic resistance of probiotic microorganisms to vancomycin. The gene encoding the type F Ddl enzyme involved in peptidoglycan modification and vancomycin insusceptibility was identified in 99% of the vancomycin-resistant strains. The study also showed that the type strain Lactobacillus thailandensis DSM 22698T was phenotypically resistant to all 16 tested antibiotics. In contrast, the strains Lactobacillus sanfranciscensis LMG 16002T and *Lactobacillus* pobuzihii NBRC 103219^T were susceptible to these antibiotics, including vancomycin [14].

Differences between phenotypic and genotypic antibiotic resistance profiles are also reflected in the results of the following study. Sixty-five strains of lactic acid bacteria (47 collection strains and 18 isolated from fermented products), including 57 strains of *Lactobacillus* (*Lactiplantibacillus plantarum* – 26, *L. fermentum* – 7, among others), were tested for susceptibility to eight antibiotics. Nearly all strains (98.5%) were resistant to ampicillin, and 96.9% wereresistant to chloramphenicol. Resistance to aminoglycosides (37%) and tetracycline (26.2%) were the most frequent phenotypes. Among the phenotypically tetracycline-resistant strains, heterofermentative lactobacilli (64%) and pediococci (100%) predominated; however, no tet genes, which confer resistance to this antibiotic, were detected in any of the strains. In *Lacticaseibacillus rhamnosus* and *L. johnsonii* strains that were phenotypically resistant to chloramphenicol, the cat gene that encodes acetyltransferase responsible for chloramphenicol resistance was also not identified [35].

An earlier study described the antibiotic resistance of 45 lactic acid bacteria strains (40 starter and 5 probiotic strains) belonging to the genera *Lactobacillus, Streptococcus, Lactococcus, Pediococcus,* and *Leuconostoc*. Antibiotic resistance was assessed using the E-test and PCR analysis with specific primers. The frequency of resistance to erythromycin, chloramphenicol, and tetracycline was low (less than 7%). In contrast, resistance to aminoglycosides (gentamicin and streptomycin) and ciprofloxacin was high (over 70%). Fifteen strains of the 45 studied contained the chloramphenicol resistance gene cat; however, all strains were phenotypically sensitive to the antibiotic. Based on PCR analysis, the authors suggested that the cat gene was not expressed in these strains [36].

Susceptibility testing was performed on 101 *Lactobacillus strains* (10 *L. acidophilus*, 31 L. amylovorus, 7 *L. crispatus*, 7 *L. gallinarum*, 26 *L. gasseri*, and 20 *L. johnsonii*) to 13 antibiotics (ampicillin, chloramphenicol, erythromycin, gentamicin, linezolid, and quinupristin/dalfopristin, among others). The analysis employed the phenotypic broth microdilution method and PCR analysis with specific primers. Phenotypic analysis revealed resistance to ampicillin, chloramphenicol, clindamycin, erythromycin, quinupristin/dalfopristin, streptomycin, and tetracycline. At the same time, corresponding resistance genes were detected in most of the resistant Lactobacillus strains, including *tetB, tetM*, and *tetO* genes associated with tetracycline resistance [37].

3) Antibiotic resistance depends on the ecological niche of probiotic microorganisms

The main ecological niches of probiotic microorganisms are the intestinal tract and fermented food products. Phenotypic and genotypic antibiotic resistance have been identified among *Lactobacillus* strains isolated from both niches [38]. *Lactobacillus* isolates obtained from fermented food products were susceptible to quinolones ciprofloxacin and gatifloxacin whereas strains isolated from the intestinal tract exhibited resistance to these antibiotics. Researchers attribute this difference to the fact that intestinal isolates, unlike those from food sources, are more frequently exposed to antibiotics used for therapeutic purposes [39].

A total of 122 strains of *Lactobacillus* isolated from homemade and commercial fermented products (yogurt and pickles), as well as 37 strains from the intestines of healthy individuals residing in Sichuan Province, China, were analyzed for antibiotic resistance. Phenotypic resistance to 17 clinically significant antimicrobial agents was assessed using the microdilution method with determination of the minimum inhibitory concentration. Antibiotic resistance was more frequently detected among intestinal isolates, whereas resistance was observed significantly less often among isolates obtained from fermented food products. This can also be explained by the fact that intestinal *Lactobacillus* strains are more frequently exposed to therapeutic antibiotics [40].

In another study, whole-genome sequencing of 401 strains of lactic acid bacteria isolated from starter cultures, probiotics, and the human gut revealed the presence of antibiotic resistance genes (ARGs) within mobile genetic elements (MGEs). The majority of ARGs (75.5%) were detected in plasmids and integrative and conjugative elements (ICEs). ARGs conferring resistance to tetracyclines, macrolides, and aminoglycosides were the most frequently identified. A comparative analysis of ARGs across the three ecological niches showed that they were most commonly found in intestinal isolates, less frequently in probiotic strains, and least often in starter cultures. According to the authors, intestinal isolates pose a significantly higher risk for horizontal transfer of ARGs via MGEs than starter or probiotic strains. Nevertheless, antibiotic-resistant strains included in probiotic formulations also require careful monitoring and analysis for the presence of MGEs capable of horizontal gene transfer within the gut microbiota [32].

4) Antibiotic resistance depends on the species/strain of probiotic microorganisms Phenotypic resistance of lactobacilli isolated from 20 patients with compromised immune status to 19 antibiotics (vancomycin, benzylpenicillin, amoxicillin, streptomycin, erythromycin, azithromycin, tetracycline, and chloramphenicol, among others) was studied using the microdilution method with the determination of minimum inhibitory concentrations (MICs). Differences in the susceptibility of lactobacilli to antibiotics were noted depending on their species affiliation. Thus, the minimum inhibitory concentrations of vancomycin, amoxicillin, and benzylpenicillin for *Lactiplantibacillus plantarum* and *Lactobacillus paracasei subsp. paracasei* were several times higher than those of *Lactobacillus acidophilus* [41].

In earlier studies, during phenotypic evaluation of antibiotic resistance in other Lactobacillus strains, high minimum inhibitory concentration (MIC) values were detected for erythromycin and tetracycline, but not for aminoglycosides [42]. Differential susceptibility among various *Lactobacillus* strains was also demonstrated with respect to macrolides. One study revealed a high level of resistance of Lactobacillus strains to macrolides [43]. In contrast, an earlier study found that the tested *Lactobacillus* strains were highly susceptible to macrolides (39). Interestingly, the overwhelming majority of the studied *L.delbrueckii* strains were susceptible to low concentrations of vancomycin. Concentrations below 1 µg/mL inhibited the growth of 92% of the investigated strains, a result that contradicts the commonly held view that lactobacilli are characterized by intrinsic resistance to this glycopeptide antibiotic [17].

A recently conducted bioinformatic analysis of resistance genes in 583 *Lactiplantibacillus plantarum* strains to macrolides, fluoroquinolones, carbapenems, and aminoglycosides based on the CARD, ARGANNOT, and ResFinder databases revealed that resistance gene profiles varied among strains. These differences concerned genes encoding enzymes that inactivate carbapenems and aminoglycosides, as well as genes activating efflux pumps responsible for the extrusion of aminoglycosides, fluoroquinolones, and macrolides from the cell. The researchers associated the involvement of specific genes in different strains with their expression activity and functional state [44].

Conclusion

Analysis of the research findings revealed significant discrepancies between the phenotypic and genotypic profiles of antibiotic resistance in probiotic microorganisms. The correlation between phenotypic and genotypic antibiotic resistance profiles ranges from high to low, depending on the nature and mechanism of action of the antibiotic, as well as on the species/strain and the ecological niche of the species.

However, there was no consistent pattern in the susceptibility of probiotic microorganisms to antibiotics associated with species/strain or ecological niche. Indeed, different studies employed various methods for phenotypic assessment of antibiotic susceptibility (e.g., minimum inhibitory concentration, the E-test, and disk diffusion assays). These methodological differences may partly explain the observed variation in the quantitative assessment of resistance levels in probiotic strains. Nevertheless, this is not the most critical factor. Unlike the fundamentally important approach of whole-genome sequencing, the need for standardized methods of phenotypic evaluation of antibiotic resistance is of comparatively lesser significance.

Many species of probiotic microorganisms with a long history of use are considered safe and are included in GRAS, QPS, and other international and national safety databases. However, when selecting or comparing a studied strain of a probiotic microorganism, it is often necessary to conduct a comprehensive analysis, and this is further complicated by the frequently low quality of the available reference databases used for comparison [45].

Our analysis of the literature revealed a consensus concerning the necessity of comprehensive safety and antibiotic resistance assessment of probiotic strains, regardless of their source of isolation (the intestinal tract, fermented products, or probiotic formulations). Strains isolated from the intestinal environment pose a greater risk in terms of harboring mobile genetic elements (MGEs) conferring antibiotic resistance, compared to those derived from fermented products. Lactic acid bacteria used in the development of probiotics are predominantly selected from the human gut, while starter cultures are typically sourced from fermented dairy products. Therefore, starter cultures carry a lower risk of containing and horizontally transferring antibiotic resistance genes [46]. At the same time, one of the most rational and accessible approaches to minimizing the risk of horizontal transfer of antibiotic resistance MGEs by probiotic microorganisms may be the selection of strains from traditional fermented dairy products.

There is a lack of research related to the horizontal transfer of antibiotic resistance genes from probiotic microorganisms to pathogens. Even when mobile genetic elements (MGEs) associated with antibiotic resistance are identified through whole-genome sequencing, there remains the question of the functionality of the detected genes.

The general consensus among authors of the reviewed publications regarding the increasing availability and promise of whole-genome sequencing (WGS) in assessing the safety and antibiotic resistance of probiotic microorganisms is further supported by the conclusions in individual studies emphasizing the necessity of analyzing the functionality and expression of resistance-determining genes. This refers to the application of metagenomic, transcriptomic, and proteomic approaches. For example, the commonly accepted notion of the intrinsic resistance of lactobacilli to vancomycin is challenged by findings indicating their sensitivity to this glycopeptide antibiotic [17]. Naturally, such results underscore the importance of conducting transcriptomic studies and metagenomic analysis to assess the potential for horizontal transfer of mobile antibiotic resistance genes [47].

The increasingly widespread use of probiotic microorganisms in medicine and veterinary practice, as well as in food and feed additives, highlights the urgency of ensuring the quality and safety of probiotics.

Authors' Contribution

KA: designed and drafted the manuscript. ZS: conducted and supervised the study. BM: conducted and translater the study. DZh: conducted the study and drafted the manuscript. ZhT: conducted the study and analysis of references. All authors have read, reviewed, and approved the final manuscript.

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