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Posted Date: 12 July 2023

doi: 10.20944/preprints202307.0741.v1

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Review

Fermented Foods as a Potential Vehicle of Antimicrobial Resistant Bacteria and Genes

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Abstract: Fermented food products are widely consumed for their nutritional and health-promoting properties earning them a central place in diets around the globe. However, these foods can present a paradox, as they have the potential to harbor not only beneficial probiotics but also antibiotic-resistant (AR) microbes and genes. The impact of AR in fermented foods has far-reaching implications, such as its potential effects on human health, repercussions in the food industry, and environmental consequences. An in-depth analysis of AR in fermented foods, including dairy products, fermented fruits and vegetables, meat products, and beverages, would provide insights into the extent and ramifications of the issue with these foods. Therefore, this review systematically presents the status of AR in fermented foods, with a particular focus on AR bacteria and genes within this category of food products. The review also highlights the complexities of AR in fermented foods, emphasizing the role of bacterial adaptation during the fermentation process and the dynamics of bacterial gene transfer. Various contributing factors to AR are brought into focus, including intrinsic resistance among bacteria in fermented foods and the potential risk of contamination with pathogenic bacteria. Moreover, this review presents a range of mitigation strategies, from the development of novel antimicrobials to advances in fermentation technology and regulatory control. This comprehensive perspective on the intricate interplay between AR and fermented food will potentially pave the way for more targeted research and mitigation strategies in this critical area.

Keywords: fermented foods; antibiotic-resistant bacteria; antibiotic-resistant genes

1. Introduction

Fermented foods have been an integral part of the global diet for centuries and are characterized by their production through controlled microbial growth and enzymatic action [1]. They encompass a wide range of food categories, including meat, dairy, vegetables, soybeans, legumes, cereals, and fruits. Fermentation serves multiple purposes, such as preservation and enhancement of organoleptic properties, offering not only unique flavors and textures but also potential health benefits. The fermentation process involves microorganisms, nutritional ingredients, and environmental conditions, resulting in numerous variations of fermented foods [2]. While fermented foods offer beneficial properties, the presence of antibiotic-resistant (AR) bacteria and genes within these food products raises concerns regarding their impact on human health. Understanding the relationship between fermented foods and AR is crucial for assessing the potential risks associated with their consumption.

Traditionally, fermentation served as a preservation method, utilizing antimicrobial metabolites to reduce the risk of contamination with pathogenic microorganisms. However, recent studies have revealed the presence of AR bacteria and genes in various types of fermented foods [3,4]. Spontaneously fermented foods pose a unique concern for AR as the presence of naturally occurring fermentative bacteria in the food matrix makes them less amenable to safety assurance measures [5]. Additionally, lactic acid bacteria (LAB), commonly found in fermented foods, have been associated with the dissemination of AR, especially when these products are consumed without heat treatment. The consumption of such foods may facilitate the exchange of functional AR genes (ARGs) between resident microorganisms and potential pathogens through horizontal gene transfer (HGT), as represented in Figure 1 [6].

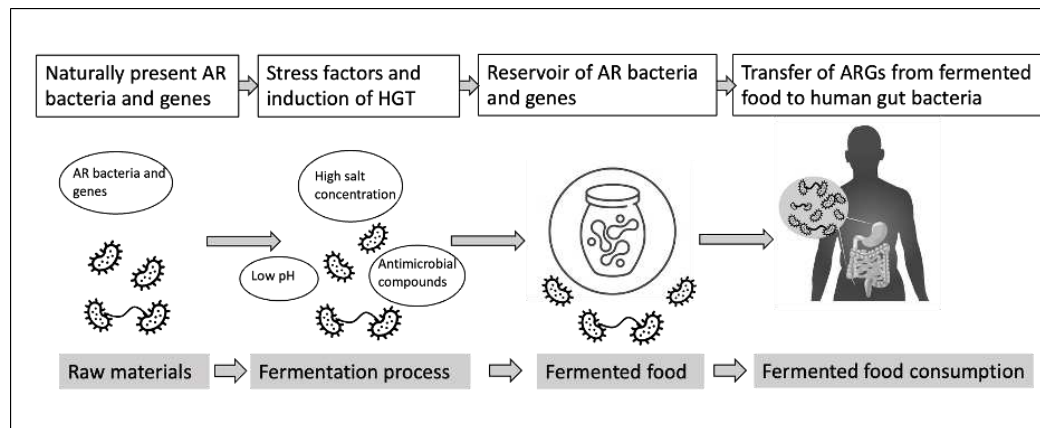


Figure 1. Potential events in fermented food production leading to the transfer of AR bacteria and genes to human gut microbiota.

Furthermore, while probiotics are generally considered safe, there have been reports of infections associated with probiotic *Lactobacilli*, particularly in immunocompromised individuals [7,8]. Alongside the possibility of probiotics being implicated in infectious processes, the concern for these bacteria acquiring resistance genes should also be addressed. In Europe, probiotics used in animal feed additives are deemed unsuitable if known exogenous resistance genes are present, especially when the acquired resistance can be further transferred [9]. By examining the presence and potential transferability of AR bacteria and genes in fermented foods, this review article aims to provide a comprehensive understanding of the implications of AR in these widely consumed products.

2. AR bacteria and genes in Fermented Foods

AR in fermented foods is a concerning phenomenon closely linked to the misuse of antibiotics in the food chain [10]. The fermentation process itself might contribute to the proliferation of bacteria, leading to an overall increase in the abundance of ARGs within fermented foods [3]. As reservoirs of AR bacteria and ARGs, fermented foods can potentially transfer these elements to other microorganisms, including pathogens. This transfer can have lasting effects on the microbial communities within the human body. Notably, fermented foods harbor a significant population of microorganisms, and the specific conditions within the fermentation environment, such as confined spaces and close cell-to-cell contact, provide an ideal setting for gene transfer. LAB and coagulase-negative *Staphylococcus* (CNS) species, commonly found in fermented foods, have been identified as carriers of ARGs, particularly against tetracyclines, penicillins, chloramphenicol, and macrolides [11]. Table 1 represents the major AR bacteria and ARGs isolated and identified from fermented foods.

In various fermented food products, metagenomic research has revealed the presence of ARGs belonging to several AR classes. Fermented dairy products exhibited an average count per million (CPM) of 3,686 ARGs per sample, while brine and sugar products had lower CPM values of 426 and 261, respectively [12]. Furthermore, using starter cultures in fermentations resulted in a five-fold higher abundance of ARGs than in spontaneous fermentations. Among 58 analyzed food samples, nine showed the presence of ARGs. These included kombucha, kefir, kimchi, pickled carrots, pickled vegetables, and apple cider vinegar samples. The presence of ARGs in fermented foods not only increases the risk of HGT but also amplifies the potential for ARG dissemination due to their mobility [12]. Therefore, understanding the prevalence and transferability of AR bacteria and genes in fermented foods is crucial for addressing the potential risks associated with their consumption.

2.1. ARGs and Associated Bacteria in Fermented Foods

2.1.1. Lactic Acid bacteria

ARGs have been consistently observed in LAB associated with various fermented foods. Specifically, resistance to tetracyclines, penicillins, chloramphenicol, and macrolides, such as erythromycin, is frequently detected among LAB strains, particularly in certain types of cheeses, fermented meats and spontaneously fermented vegetables [13,14]. In studies analyzing LAB isolates from Indonesian traditional fermented foods (dadih, tape ketan, bekasam, and tempoyak), a significant number of strains were found to be resistant to chloramphenicol and erythromycin [15]. *Lactobacilli*, commonly used as starter cultures in fermented milk products, exhibit widespread resistance to penicillins. Studies have identified acquired resistance of LAB to tetracycline, erythromycin, clindamycin, and chloramphenicol in *Lactobacilli* isolated from fermented foods. The resistance is mediated by specific genes such as *tetM* and *tetS* (associated with tetracycline resistance) and *erm(B)* (associated with erythromycin resistance). Furthermore, the *cat* gene, encoding chloramphenicol acetyltransferase and carried on plasmids, has been identified as a resistance determinant in those isolates [16,17].

In a study examining 16 fermented Chinese foods and eight sausages and pickles, LAB isolates displayed varying levels of AR. LABs in pickle samples showed susceptibility to tetracycline, ampicillin, and clindamycin but showed resistance to other antibiotics. LABs in sausage samples from different provinces also exhibited differing levels of resistance, with some strains showing resistance to multiple antibiotics [18]. PCR analysis of antibiotic-resistant LAB strains revealed the presence of frequently detected ARGs, such as *ermB*, and *tetM*, found on both plasmid and chromosomal DNA. *tetM* gene was consistently identified in all tetracycline-resistant LAB strains, with some strains carrying the gene on both plasmids and chromosomes, indicating multiple mechanisms and locations for ARG occurrence [18]. Additionally, certain strains of *Lactobacillus delbrueckii subsp. bulgaricus*, commonly used in yogurt cultures, demonstrated intrinsic resistance towards mycostatin, nalidixic acid, neomycin, polymyxin B, trimethoprim, colimycin, sulfamethoxazole, and sulphonamides [19].

2.1.2. Staphylococcus spp.

Coagulase-negative *Staphylococcus* (CNS) species, frequently found in fermented animal products such as certain meats, cheeses, and fermented fish products, have been associated with the presence of ARGs. The common ARGs include resistance to tetracyclines, penicillins, chloramphenicol, and macrolides [20].

In a Swiss study, tetracycline resistance was detected in *Staphylococcus* isolates used as starter cultures in meat, as well as in *Bifidobacterium lactis* and *Lactobacillus reuteri* [21]. Another study conducted in Nigeria examined 255 CNS isolates obtained from six different Nigerian fermented foods (including kindirmo, nono, iru, wara, ogi, and kunu) and found that a substantial proportion of the isolates exhibited resistance to different antibiotics. Specifically, a high percentage of isolates demonstrated resistance to ampicillin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, and oxacillin. *Staphylococcus caprae* showed particularly high resistance levels to multiple antibiotics, including ciprofloxacin, ofloxacin, gentamicin, erythromycin, and cefotaxime [22]. In yet another study, the genetic diversity and AR profiles of *Staphylococcus saprophyticus* isolates from fermented foods and clinical samples were assessed, revealing notable resistance rates to lincomycin, erythromycin, and tetracycline [23].

2.1.3. Enterococcus spp.

Enterococcus species, commonly found in Turkish white cheese, have exhibited resistance to streptomycin, erythromycin, oxacillin, and vancomycin. In fact, a high prevalence of vancomycin resistance was observed in *Enterococcus faecalis* (96.8%) and *Enterococcus faecium* (76%) isolates [24]. The presence of specific resistance genes in *Enterococcus faecium* strain SZ109 was also investigated, with the *ermB* gene associated with erythromycin resistance, detected on both the plasmid and

chromosome. Additionally, the *aphA3* gene, conferring resistance to antibiotics like kanamycin and neomycin, was exclusively found on the plasmid, while the *mefA* gene, responsible for macrolide resistance, was exclusively located on the chromosome [18]. A comprehensive study assessed the resistance patterns of 55 *Enterococci* strains, including 41 *Enterococcus faecium* and 14 *Enterococcus faecalis* strains, isolated from various traditional fermented foods of animal and vegetable origins, as well as water samples. The analysis revealed that certain strains exhibited resistance to vancomycin, while a high incidence of AR was detected among *Enterococcus faecalis* isolates to rifampicin, ciprofloxacin, and quinupristin/dalfopristin. Intermediate resistance to erythromycin and tetracycline was also observed. Among *Enterococcus faecium* isolates, resistance was found against rifampicin, ciprofloxacin, erythromycin, levofloxacin, and nitrofurantoin [25]. These findings underscore the presence of AR in *Enterococcus* species isolated from fermented foods and emphasize the importance of understanding and monitoring their resistance profiles for food safety and public health considerations.

Table 1. Antibiotic-resistant bacteria and antibiotic-resistant genes in fermented foods.

| Food type | Bacteria present | ARGs | Reference |
|------------------------|----------------------------------|--|------------|
| Cheese | LAB, <i>Staphylococcus</i> (CNS) | Tetracycline, Chloramphenicol, erythromycin | [13,14] |
| Fermented meat/sausage | LAB, <i>Staphylococcus</i> (CNS) | Tetracycline, Chloramphenicol, erythromycin, Penicillins | [11] |
| | <i>Salmonella</i> | Amoxicillin, Gentamycin, Streptomycin, tetracycline | [14] |
| | <i>Listeria monocytogenes</i> | Amoxicillin, benzyl penicillin, tetracycline, ciprofloxacin | [14] |
| Fermented vegetables | LAB | Tetracycline, Chloramphenicol, erythromycin, Clindamycin | [11,13,14] |
| Yogurt | <i>Lactobacillus</i> | Mycostatin, nalidixic acid, neomycin, polymyxin B, trimethoprim, colimycin, sulfamethoxazole, and sulphonamides | [19] |
| | <i>Streptococcus</i> | Colimycin, gentamicin, kanamycin, mycostatin, nalidixic acid, neomycin, polymyxin b, trimethoprim/sulfamethoxazole, streptomycin, and sulfonamides | [19] |
| Vinegar | Acetic acid bacteria | Trimethoprim, ciprofloxacin, erythromycin | [26] |
| Turkish cheese | <i>Enterococcus</i> | streptomycin, erythromycin, oxacillin, and vancomycin | [24] |
| Fermented fish | <i>Staphylococcus</i> (CNS) | tetracyclines, penicillins, chloramphenicol, and macrolides | [20] |

2.1.4. AR genes in Other Bacteria

Research has focused on AR in *Acetobacter* and *Komagataeibacter* species, predominantly derived from vinegar, revealing resistance to trimethoprim, erythromycin, ciprofloxacin, and chloramphenicols [26]. Another study investigating AR microorganisms in meat and minced meat used for fermented sausage production found *Salmonella* strains exhibiting resistance to amoxicillin

(44.5%), gentamycin (38%), streptomycin (44.5%), and tetracycline (55.5%). Similarly, *Listeria monocytogenes* displayed resistance to amoxicillin (38.5%), benzylpenicillin (30.8%), tetracycline (53.8%), and ciprofloxacin (38.5%). *Escherichia coli* strains showed resistance to amoxicillin (33.3%), neomycin (30%), streptomycin (40%), and tetracycline (40%) [14]. Moreover, fifteen strains of *Streptococcus thermophilus* isolated from yogurt cultures exhibited varying levels of resistance to colimycin, gentamicin, kanamycin, mycostatin, nalidixic acid, neomycin, polymyxin B, trimethoprim/sulfamethoxazole, streptomycin, and sulfonamides [19]. Furthermore, high tetracycline and erythromycin resistance occurrences have been observed in *Lactococcus* and *Streptococcus thermophilus* strains isolated from dairy products [21]. These findings highlight the prevalence of AR in diverse bacterial species associated with fermented foods and accentuate the need for continued surveillance and management strategies to mitigate the risks posed by AR strains.

3. Role of Bacterial Adaptation and Gene Transfer in Fermented Foods

Fermented foods comprise a complex micro-environment characterized by diverse microbial communities, creating an ideal environment for horizontal gene transfer [27]. HGT in fermented foods plays a crucial role in the adaptation of bacteria to evolving nutritional needs and environments [28]. For example, during the fermentation process of foods such as cheese, wine, yogurt, and vinegar, the acquisition of the horizontal transfer region occurs, facilitating the transfer of genetic material among microbial populations [29]. This can potentially improve the quality and shelf life of fermented foods. Research shows that the occurrence of HGT in a specific environment is beneficial for starter culture domestication; a process that involves selectively cultivating and adapting specific microorganisms to exhibit desired traits and behaviors during the fermentation process, leading to improved fermentation efficiency, digestibility, palatability, and longevity [29,30]. Microbial fermentation leading to HGT in fermented beverages, such as wine and beer, has also been reported, potentially impacting their shelf life and sensory attributes [31]. However, it is important to note that while HGT contributes to the adaptation and quality of fermented food, it can also facilitate the transfer of ARGs among microbial populations [3]. Within the fermentation environment, microbial interactions, such as conjugation or transduction, may also occur during manufacturing and storage [32].

3.1. Horizontal Gene Transfer in Fermented Food

The transfer of ARGs through HGT in fermented foods has been extensively studied, with sausages, kefir, yogurt, and cheese being key examples. These studies also highlight the potential of ARG transmission to both animal and human microbiota. Leroy et al, observed the transfer of plasmids carrying ARG during sausage fermentation involving *Staphylococcus xylosus*, isolated from fermented sausage [33]. Furthermore, the analysis of mobile genetic elements (MGE) domains in kefir revealed the presence of ARG *lmrD* (provides resistance to lincosamides). The contig containing this gene was found in close proximity to a transposase open reading frame (ORF) within ten neighboring ORFs, suggesting potential gene mobility in the fermentation-associated microbial community [3]. Metagenomic analysis of fermented milk products such as yogurt, nunu, kefir, and Koumiss demonstrated the presence of plasmid-borne ARGs within the fermented milk microbiome [34]. Additionally, plasmid-mediated transfer of AR has been demonstrated between strains of *L. curvatus* during sausage fermentation [35]. The ripening of fermented sausages also facilitates a high frequency of plasmid transfer among *Enterococcus faecalis* strains, highlighting the close contact and genetic transfer facilitated during the ripening of sausages [36]. Cheese, known for its favorable conditions for microbial survival and growth, can harbor AR pathogens such as *Listeria* due to its moderately high-water activity and low salt content and serve as a potential reservoir for the acquisition of resistance genes by *Enterococci*. The horizontal transfer of the *tetM* gene from *L. monocytogenes* to *E. faecalis* was investigated in Minas Frescal cheese. The results revealed that both donor and recipient strains remained viable throughout the 21-day shelf life, with transconjugant bacteria detected from the second day onwards [37]. Commercial dairy-derived *Lactobacillus* strains from cheese and yogurts carried plasmid-mediated streptomycin and gentamicin resistance genes in

L. rhamnosus and *L. plantarum*, indicating the potential for HGT among probiotic strains [38]. During soybean fermentation, a plasmid carrying a lincosamide resistance gene (*lnuA*) was transferred between coagulase-negative *Staphylococci* in the presence of lincomycin. Interestingly, the plasmid was efficiently transferred between these bacteria during passage through murine intestines, even in the absence of lincomycin, highlighting the enhanced transferability under in vivo conditions [39]. A similar study conducted by Li et al., [40] reported the transfer of *vanA* gene associated with vancomycin resistance during the early stages of fermented soybean meal (FSBM) production, with transconjugants steadily increasing throughout the fermentation process. Notably, these transconjugants were able to pass through the digestive tract of growing pigs and detected after three days of feeding. These findings underscore the potential dissemination of ARGs carried by commercial probiotics used in animal feed and feed additives within the digestive tracts of animals. Such dissemination poses a risk of further infections under extreme conditions, highlighting fermented food as a potential source of ARGs to human gut microbiota via HGT.

3.2. Stress Response Contributing to Gene Transfer

During fermentation, bacteria encounter various stressors such as low pH, high salt concentration, and the presence of antimicrobial compounds produced during the fermentation process. These stressors may exert selective pressure on bacterial populations, leading to the survival and proliferation of adapted strains. Some bacteria possess intrinsic mechanisms to counteract these stresses, while others may acquire adaptive traits through HGT. Stressful conditions, such as low temperatures, can favor the transfer of genetic elements, including ARGs [41,42]. LAB, predominantly found in cold dairy environments, has been frequently linked with AR. In the case of cheese, temperature, and pH influenced antibiotic gene transfer. At a processing temperature of 30°C, the highest levels of donor and recipient bacteria were observed after 48 hours, while transconjugant bacteria peaked at 48 hours. At 10°C, growth rate and acidification were reduced, resulting in delayed detection of vancomycin-resistant transconjugants that reached their highest number during ripening [36]. Furthermore, Tarrah et al [43] discovered a genomic island closely associated with *S. thermophilus* isolated from dairy environments, containing the *tetS* gene, along with genes related to plasmids, beta-lactamase class C-like, and penicillin-binding proteins superfamily. However, no HGT was detected from *S. thermophilus* to *L. rhamnosus* and *L. delbrueckii* during skim milk fermentation, refrigerated storage, and simulated gastrointestinal transit. On the other hand, the transfer frequencies of tetracycline, ampicillin, and chloramphenicol resistance genes significantly increased following high-pressure processing exposure, commonly used in the preservation of fermented food, both in vitro and in the food matrix, when compared to the non-pressurized control strains [44]

3.3. Transfer of ARGs from Fermented Food to Human Microbiota

Transfer of ARGs within fermented foods presents a dual concern, as they impede microbial evolution within the food matrix while also posing a risk to human health. Bacteria that enter our gut through food intake have the potential to exchange functional ARGs with both saprophytic bacteria and nearby pathogens through HGT, leading to the emergence of resistant or multi-resistant pathogenic strains limiting treatment options for infections [3]. The consumption of livestock products facilitates the establishment of transfer connections between bacteria, as it brings bacterial populations harboring diverse sets of ARGs [3]. *Lactobacilli*, due to their wide environmental distribution, can act as potential vectors for the dissemination of AR, raising concerns about their use as probiotics due to the acquisition and transfer of transferable AR determinants [45]. Previous research has demonstrated the transfer of ARGs between *Lactobacillus* species and even to other pathogens. Transfer of vancomycin resistance from *Enterococci* (both of human and animal origin) to a probiotic *Lactobacillus acidophilus* was observed in vitro and in vivo in mice, highlighting the potential long-term consequences of accumulating ARGs in the gut [45]. Given the high frequency of transfer of resistant determinants in mouse models, it is likely that similar events occur in the human gut, which serves as a reservoir for ARGs [46]. Consumption of fermented products in conjunction

with appropriate triggers further increases the potential for HGT within the human gut [3]. *Enterococci*, known for causing human diseases, possess acquired antibiotic resistance along with intrinsic resistance to multiple antibiotics, low pH, high salt concentrations, and high temperatures, enabling their survival in harsh environments. AR *Enterococci* are commonly found in animal-derived foods and thrive during sausage fermentation. Transfer of tetracycline-resistant determinant *tet*(M) from *E. faecium* isolated from dry sausage to clinical isolates of *E. faecalis* and *E. faecium* was associated with the type 1 Integron [4], highlighting the significance of fermented food as reservoirs of ARGs and their potential transfer to human strains upon consumption.

4. Other Contributing Factors to AR in Fermented Food

Lactobacillus species, commonly used in the fermentation process, exhibit both acquired and intrinsic resistance to antibiotics, raising concerns about their safety in food products. Intrinsic resistance, unique to this bacterial group, varies among species [19]. LAB demonstrates natural tolerance to a range of antibiotics, including bacitracin, cefoxitin, ciprofloxacin, fusidic acid, gentamicin, metronidazole, nitrofurantoin, norfloxacin, sulphadiazine, teicoplanin, trimethoprim/sulfamethoxazole, kanamycin, streptomycin, and vancomycin [17,19]. Specifically, *L. rhamnosus* strains isolated from Parmigiano Reggiano cheese showed tolerance to aminoglycosides, glycopeptides, and quinolones [5,47]. Some *Lactobacillus* species used as probiotics are intrinsically resistant to vancomycin and aminoglycosides, where the mechanism of vancomycin resistance is well characterized [48]. Vancomycin interacts with peptidoglycan precursors that are found on the cell wall side of the membrane of the cytoplasm and bind onto the D-alanine/D-alanine terminal of the pentapeptide, blocking peptidoglycan precursor polymerization. In certain LAB species, the terminal D-alanine residue in the muramyl pentapeptide is changed by D-lactate or D-serine, blocking vancomycin binding and thus developing resistance to the antibiotic [49]. Similarly, *Leuconostoc* and *Pediococci* isolated from alcoholic beverages and food products exhibited vancomycin resistance [19,50].

Moreover, numerous *Lactobacillus* species were intrinsically resistant to aminoglycosides, including gentamicin, kanamycin, streptomycin, neomycin, ciprofloxacin, and trimethoprim [51,52]. *Lactobacillus rhamnosus*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus* and *L. helveticus* lack cytochrome-mediated drug transport, rendering them intrinsically resistant to aminoglycosides [6,47]. Folate auxotrophic *Lactobacilli*, such as *L. acidophilus*, *L. salivarius*, *L. johnsonii*, *L. brevis*, *L. casei*, *L. rhamnosus*, *L. delbrueckii*, *L. gasseri*, *L. fermentum*, *L. plantarum*, *L. reuteri*, *L. sakei*, *L. helveticus*, and *L. crispatus*, were found to be intrinsically resistant to trimethoprim [51,53].

Similarly, *Bifidobacterium* obtained from probiotic cultures exhibited resistance to vancomycin, gentamicin, kanamycin, streptomycin, fusidic acid, trimethoprim, norfloxacin, nalidixic acid, metronidazole, polymyxin B, and colistin, although the mechanisms of resistance remain unknown [54]. In naturally fermented Aloreña table olives, *Lactobacillus pentosus* and *Leuconostoc pseudomesenteroides* strains showed intrinsic resistance to vancomycin, teicoplanin, streptomycin, kanamycin, and trimethoprim/sulfamethoxazole. This multi-resistance may be attributed to chromosomally encoded efflux pumps coded by *norA*, *mepA*, and *mdeA* genes [55].

Among LAB, *Enterococci* are intrinsically resistant to cephalosporins, low levels of clindamycin, and aminoglycosides in milk and meat samples [56]. High-level gentamicin resistance was observed in many dairy isolates, despite their intrinsic resistance to low levels of gentamicin (17). *Enterococcus faecium* strain 68, used as a probiotic for humans and animals and as a silage inoculant, was found to be intrinsically resistant to kanamycin, streptomycin, and oxacillin [19]. *Lactococcus lactis* was recorded to be naturally resistant to colistin, fosfomycin, pipemidic acid, and rifamycin [57]. From different strains obtained from yoghurt culture, 31 strains of *Lactobacillus delbrueckii* subsp. *bulgaricus* seemed to be intrinsically tolerant to mycostatin, nalidixic acid, neomycin, polymyxin B, trimethoprim, colimycin, sulfamethoxazole, and sulphonamides. Susceptibilities to cloxacillin, dihydrostreptomycin, doxycycline, furadantin, novobiocin, oleandomycin, oxacillin, and streptomycin [58].

5. Mitigation strategies

The presence of AR bacteria and genes in fermented foods raises concerns regarding their impact on human health. To mitigate these risks, several strategies can be implemented in the production and consumption of fermented foods (Figure 2), which are described below:

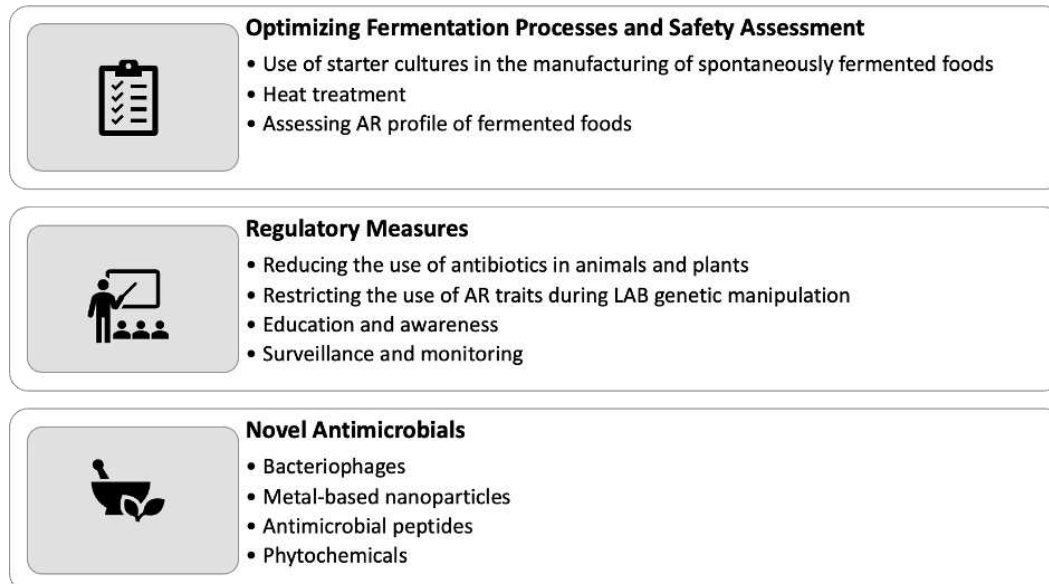


Figure 2. Strategies for reducing AR in fermented food production.

5.1. Optimizing Fermentation Processes and Safety Assessment

Implementing starter cultures during the manufacturing process of spontaneously fermented plant-based foods can effectively manage AR [59]. Recent advancements enable the use of multi-strain starters comprising microorganisms unique to these foods, allowing for better control over fermentation outcomes [60]. However, it is important to note that the use of starter cultures may result in the loss of some organoleptic properties associated with natural fermentation. Another approach to managing AR in fermented foods is through the application of heat treatment or pasteurization techniques, which can diminish or eradicate microorganisms, including AR strains [5,61]. Nevertheless, it is essential to consider that these methods may impact the organoleptic qualities, live microbial content, and potential health benefits associated with live microbes in the final product. Assessing antibiotic susceptibility within the diverse bacterial community present in fermented foods is crucial for ensuring food safety. While culture-dependent methods have limitations in detecting low-frequency resistance genes due to the vast number of uncultured microorganisms, high-throughput technologies such as metagenomics offer a culture-independent approach [52,62]. Metagenomics enables the identification of uncultured bacteria, the detection of novel AR genes and gene transfer methods, and the comprehensive safety assessment of traditional fermented foods [52]. It is important to note that AR evaluation should not be confined to PCR detection of known AR genes but should also involve genome sequencing to discover and describe novel AR genes and transfer mechanisms [63]. In addition to the strategies mentioned above, integrating other measures can further contribute to controlling AR in fermented foods. These may include implementing stringent hygiene practices, optimizing fermentation conditions, and adopting good manufacturing practices, which indirectly affect the microbiota associated with fermented foods.

5.2. Regulatory Measures for Combating AR in Fermented Foods

A key mitigation strategy for addressing AR in fermented foods involves implementing regulatory changes at various levels. One crucial step is to reduce AR in food animals and plants

through the cautious use of antibiotics. Additionally, it is essential to restrict the use of antibiotics that can potentially lead to cross-resistance to compounds used in human medicine, such as tylosin and virginiamycin, to control the transfer of ARGs [19]. In the field of genetic manipulation of LAB, AR traits are being replaced with selectable indicators for various purposes, including the development of food-grade vectors. This shift aims to avoid undesirable resistance transfer or conferment to endogenous bacteria. While it is possible to generate AR probiotics by introducing diverse resistance to bacteria, it is crucial to ensure that probiotics do not carry more resistance than necessary for their intended purpose [19]. To guarantee the safety of probiotic lactic acid bacteria (e.g., *Lactobacilli*, *Lactococci*, *Enterococci*, and *Bifidobacteria*) for human consumption, strict adherence to safety and quality standards, guidelines, and regulations is essential throughout the pre-and post-marketing stages. Robust measures should be in place to assess and monitor the biosafety of probiotic strains, ensuring their suitability for use in food products. This includes a comprehensive evaluation of their antibiotic resistance profiles to prevent the dissemination of resistant strains [19]. Regulatory initiatives should also focus on promoting responsible antibiotic use across the entire food production chain. This involves educating and raising awareness among stakeholders about the potential consequences of antibiotic misuse and overuse. Encouraging the adoption of alternative disease prevention and treatment methods, such as vaccination, probiotics, and phage therapy, can help reduce reliance on antibiotics and mitigate the emergence and spread of AR. Implementing robust surveillance and monitoring systems is crucial for tracking the prevalence and trends of AR in fermented foods. This includes regular monitoring of antibiotic residues, microbial quality, and resistance profiles in raw materials, production processes, and finished products. Prompt detection and response to emerging AR threats can enable timely intervention and the development of targeted control strategies.

5.3. Novel Antimicrobials

As AR continues to pose a significant health concern, the urgent need for novel therapeutic alternatives and alternative antimicrobial therapies that are less prone to developing resistance becomes paramount. One promising approach involves the use of bacteriophages, metal-based nanoparticles, antimicrobial peptides, phytochemicals, antibodies, and gene-based CRISPR methods [64]. These innovative strategies offer diverse mechanisms of action and can target specific pathogens or resistance mechanisms, providing potential solutions to mitigate antibiotic resistance in fermented foods. Utilizing natural plant-derived compounds is a particularly promising avenue for controlling microorganisms and combating AR. Compounds such as trans-cinnamaldehyde, eugenol, thymol, carvacrol, resorcylic acid, and caprylic acid exhibit strong antibacterial action [65]. For instance, extracts from cloves and cinnamon have been reported to possess anti-listerial effects in cheese, highlighting the potential of these natural compounds as alternatives to traditional antibiotics [65]. In addition to the mentioned antimicrobial strategies, other novel approaches are being investigated to combat antibiotic resistance in fermented foods. These include the development of engineered probiotics capable of producing antimicrobial compounds, the application of CRISPR-Cas technology to selectively target and eliminate ARGs, and the use of advanced delivery systems to enhance the efficacy of antimicrobial agents [66,67]. By exploring and harnessing these cutting-edge techniques, the food industry can find effective means to counteract antibiotic resistance and ensure the safety and quality of fermented food products.

Given the complex nature of AR, a comprehensive approach that integrates multiple mitigation strategies is crucial. This includes combining traditional control measures, regulatory changes, novel antimicrobials, and innovative technologies to create a multifaceted approach that addresses the diverse challenges posed by antibiotic resistance in fermented foods. Collaboration between researchers, food producers, regulatory bodies, and healthcare professionals is vital to drive innovation, foster knowledge exchange, and develop effective strategies that can successfully mitigate antibiotic resistance in the food industry. By incorporating novel antimicrobials, exploring natural compounds, and adopting innovative approaches, the food industry can make significant strides in combating antibiotic resistance in fermented foods. These strategies not only contribute to

safeguarding public health but also promote the sustainability and long-term viability of the fermented food sector.

5. Conclusions and Future Directions

Given the complex nature of AR, a comprehensive approach that integrates multiple mitigation strategies is crucial. This includes combining traditional control measures, regulatory changes, novel antimicrobials, and innovative technologies to create a multi-faceted approach that addresses the diverse challenges posed by antibiotic resistance in fermented foods. Collaboration between researchers, food producers, regulatory bodies, and healthcare professionals is vital to drive innovation, foster knowledge exchange, and develop effective strategies that can successfully mitigate antibiotic resistance in the food industry. By incorporating novel antimicrobials, exploring natural compounds, and adopting innovative approaches, the food industry can make significant strides in combating antibiotic resistance in fermented foods. These strategies not only contribute to safeguarding public health but also promote the sustainability and long-term viability of the fermented food sector.

Author Contributions: Writing—original draft preparation, P.G.V., L.S.V., D.J. and K.V.; writing—review and editing, P.G.V., L.S.V., D.J. and K.V.; visualization, P.G.V. and K.V.; supervision, K.V. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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