Antimicrobials and Food-Related Stresses

Subjects: Agriculture, Dairy & Animal Science | Food Science & Technology | Microbiology
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Ultraviolet (UV) radiation uses physical energy, and it is a non-thermal and non-chemical technology used by the food industry for liquid and solid surface decontamination, to control foodborne pathogens and spoilage microorganisms, as well as viruses and protozoa. UV radiations at short wavelengths, in the range of from 220 to 280 nm, result in physical damage to the nucleic acids and inhibit bacterial replication by induction of the formation of cyclobutene pyrimidine dimers, which blocks DNA replication and transcription, leading to cell death . However, the repair mechanism of UV damage, especially by photoreactivation, is a major disadvantage of UV disinfection .

Keywords: antimicrobial resistance ; food chain ; stressors ; cross-resistance ; adaptive response

1. Introduction

In recent years, there has been an effort to reduce foodborne diseases, by the implementation of food safety measures from farm to fork. Nonetheless, a high burden of foodborne diseases still exists, with the World Health Organization estimating that each year worldwide, the consumption of unsafe food causes about 600 million cases of foodborne diseases and 420,000 deaths [1]. Further, amongst the cases of foodborne diseases, the ones caused by antibiotic-resistant bacteria are increasing and are a major health problem, with the food chain being pointed to as a relevant vehicle of antibiotic resistance to humans [2].

The use and misuse of antimicrobial compounds have been related to an increase in the emergence of antimicrobial resistance (AMR) amongst foodborne microorganisms. The identification of resistant microorganisms at every stage of the food chain, from farm to fork, highlights the major concern that is AMR [2][3]. biocides are considered as a key motive power for the emergence and spread of antibiotic resistance along the food chain [4]. However, other factors, such as different antimicrobial approaches, or even agricultural or food-processing procedures, may have a role in the emergence and spread of antibiotic resistance along the food chain.

During food production and processing, different types of antimicrobials are used throughout the several stages of the food chain, namely, antibiotics, agricides and biocides, among others (e.g., agrochemicals, feed and food preservatives, decontaminants, or disinfectants). These products are applied to ensure food quality and safety, as well as to assure the efficiency of the system. Antimicrobials may also be added to feed and food as preservatives to control foodborne bacteria, inhibit spoilage microorganisms, and extend the shelf life of the final products. Decontaminants can be used to inactivate, or inhibit, the growth of pathogenic and spoilage microorganisms in fresh food, while disinfectants are mostly used to reduce the level of microorganisms in abiotic surfaces, equipment, and others [4][5].

Overall, foodborne bacteria are subject to several stresses during their lifecycle, and throughout all the processes associated with food production, processing and storage. The adaptative or protective response may, in turn, confer protection to the same stress or against a different type of stress, known as stress cross-adaptation [6]. Usually, this adaptation occurs as a cellular response of the bacterium to the stressor, by regulating molecular mechanisms that, ultimately, may result in the cellular repair or damage tolerance, in the maintenance of cell homeostasis, or even in the removal of the stressor [6][7]. In turn, this cross-adaptation may select variants with increased tolerance or resistance, including decreased susceptibility to several antibiotics, namely, some antibiotics relevant to clinical practice.

Taking this into consideration, this review focused on the cross-adaptation due to the non-antibiotic, food-chain-related stresses, associated with a diminished susceptibility to antibiotics and facilitation of antimicrobial emergence, and, thus, the spread of antibiotic resistance along the food chain, while also acting as an AMR reservoir.

2. Interaction of the Use of Non-Antibiotic Antimicrobials with A Potential Antibiotic Decreased Susceptibility

A further driver of resistance is the non-antibiotic antibacterial, such as agrochemicals, biocides, heavy metals, or food preservatives, for which bacteria could acquire antibiotic resistance by co- or cross-resistance mechanisms.

Furthermore, the presence of a diversity of drugs, commonly used in humans and animals, as well as on agricultural procedures, in surface and wastewaters, even in trace amounts, may enter the food chain and potentiate the development of resistant foodborne pathogens. They found that the exposure to organophosphates led to substantive changes in the minimum inhibitory concentration (MIC) values of the antibiotics tested (ampicillin, erythromycin, gentamicin, kanamycin, neomycin, norfloxacin, oxacillin, sulfathiazole, tetracycline, and vancomycin). When agrochemical combinations were applied, a major increase in MICs to all tested antibiotics was presented [8]. The potentiation of decreased susceptibility to antibiotics by exposure to a mixture of pesticides or pesticides and antibiotics has been reported by other authors [9].

In fact, the induced response to the various herbicides varied according to the exposed species, and the tolerance to different antibiotics changed with the exposure to different herbicides. In fact, historical isolates of S. enterica from a period before the introduction of the glyphosate-based herbicides presented lower MICs for these compounds than isolates collected after the introduction of the herbicide [10]. S. enterica presented a slow adaptation dynamic; however, glyphosate-based herbicide resistance has the potential to become fixed in isolates, with mutations arising close to or at the glyphosate molecular target, as well as in genes associated with stress response and tolerance [11]. The transient exposure of pathogenic S. enterica strains to sub-inhibitory concentrations of the herbicide elicited a tolerance response at the cellular level and up-regulation of the AcrAB-TolC efflux system.

Other chemical stressors, such as pesticides, have also been shown to influence the expression of genes coding for efflux or influx proteins. Consequently, environmental contamination with pesticides may be associated with antibiotic resistance. However, it was used for many years as a bactericide, fungicide, herbicide, defoliant, and wood preservative, and can still be detected in food products [12][13]. This compound was shown to upregulate genes coding for multidrug efflux pumps, including MexAB-OprM, an efflux pump responsible for resistance to a wide variety of antibiotics in Pseudomonas aeruginosa (P. aeruginosa) [14].

In the case of the first scenario, the higher resistance to streptomycin was attributed to mutations associated with the antibiotic target by exposure to the pesticides. In the second scenario, diverse genetic mutations emerged from exposure to both pesticides and ampicillin, with the ones differing from the mutants resulting from ampicillin exposure, which were transcriptional-level associated. These mutations suggest that higher resistance may be gained by augmented biofilm formation, heat shock, oxidative stress or carbon starvation defenses, and the deactivation of prophage related genes. The authors proposed that the co-occurrence of pesticides and sub-inhibitory concentrations of antibiotics select, de novo, antibiotic-resistant mutants from a susceptible population in a synergistic way, leading to a higher resistance than from mutants, selected by only the antibiotic [15].

Beyond the role of the adaptative response triggered by exposure to agrochemicals leading to changes in gene expression, often associated with efflux and permeability or phenotypical resistance, the acquisition of spontaneous mutations has also been related to a decrease in susceptibility to antibiotics, and attention must be given to co-resistance occurrence.

Overall, these works pointed to the significance that low-level chemical contaminations may have in decreasing the susceptibility to antibiotics, even at legal food residue levels, while highlighting the need for further study.

Another important factor involved in the development of antibiotic resistance is the extensive and widespread use of biocides in the food and health system and animal facilities. Therefore, there are large amounts of residuals of these compounds in the sewage, water from agricultural areas and other similar aquatic environments. Sometimes, co- or cross-selection with other biocides or antibiotics can also occur [16][17][18]. Several researchers proposed that some biocides can provide cross-resistance properties to antibiotics, including: triclosan; chlorhexidine; hypochlorite; chlorine dioxide; quaternary ammonium compounds (QACs); parabens; phenols; glutaraldehyde; acid anionics; peroxygen compounds (Table 1).

Table 1. Examples of bacterial cross-adaptation to antibiotics induced by exposure to non-antibiotic antimicrobials.

Non-Antibiotic Antimicrobials	Bacterial Species	Antibiotics to which Susceptibility was Decreased	Bacterial Adaptation/Mechanism of Resistance	Reference
Agrochemicals				
Combination of three pesticides: captan, carbaryl, and malathion	*S. aureus*	Sulfamethazine	Not reported	[11]
Dicamba		Chloramphenicol, ciprofloxacin, tetracycline/ Ampicillin, chloramphenicol, ciprofloxacin, tetracycline		
2,4-dichlorophenoxyacetic acid	*E. coli*/ *S.* Typhimurium	Ampicillin, ciprofloxacin/ Ampicillin, chloramphenicol, ciprofloxacin, tetracycline	Efflux pumps and induction of the *soxRS* regulon account for the change in susceptibility in *E. coli*. Dicamba plus chloramphenicol and Roundup plus kanamycin	[12]
Glyphosate (RoudUp)		Ciprofloxacin/ Ciprofloxacin, kanamycin		
Mixture of 23 pesticides	*E. coli*	Streptomycin	Mutations associated with the antibiotic target	[13]
Biocides				
Sodium hypochlorite	*E. coli*	Spectinomycin, nalidixic acid, ampicillin-sulbactam	Increase in cell surface hydrophobicity and biofilm formation, changes in cell morphology and ultrastructure	[14]
Quaternary ammonium disinfectant or triclosan	*S.* Typhimurium	Chloramphenicol, ciprofloxacin, tetracycline, ampicillin	Overexpression of AcrAB efflux pump and reduction in outer membrane porins	[15]
Triclosan	*E. coli*	Ampicillin, ampicillin-sulbactam, cefazoline, cefaclor, cefotaxime, cefepime, erythromycin, azithromycin, gentamicin, chloramphenicol, tetracycline, ciprofloxacin, lomefloxacin, imipenem	Changes in bacterial membrane properties and enhancing the efflux system	[16]
Quaternary ammonium disinfectant	*S. aureus*	Fluoroquinolones	Increased expression of *norA*	[17]
Quaternary ammonium disinfectant (benzalkonium chloride)	*L. monocytogenes*	Cefotaxime, cephalothin, ciprofloxacin	Increased expression of MdrL efflux pump	[18]
Benzalkonium chloride or chlorhexidine	*P. aeruginosa*	Ciprofloxacin, novobiocin	Decrease in the expression of the repressor gene *mexR* and increase the activity of MexAB-OprM and MexCD-OprJ efflux pumps	[19,20]

Non-Antibiotic Antimicrobials	Bacterial Species	Antibiotics to which Susceptibility was Decreased	Bacterial Adaptation/Mechanism of Resistance	Reference
Agrochemicals				
Didecyldimonium chloride	*P. aeruginosa*	Colistin, ceftazidime, amikacin, meropenem, gentamicin, piperacillin-tazobactam, ciprofloxacin	Not reported	[21]
Sodium hypochlorite	*P. aeruginosa*	Amikacin, gentamicin, meropenem, ciprofloxacin	Not reported	[21]
Chlorhexidine	*K. pneumoniae*	Colistin	Mutations in Tet repressor gene (*smvR*) and up-regulation of the *smvA* gene, both involved in MFS efflux pump system; modification of LPS	[22]
Chlorine	*Salmonella* Enteritidis	Tetracycline, nalidixic acid, chloramphenicol	MarRAB operon and increased expression of efflux pumps	[23]
Chlorine	*S. enterica* serovar Heidelberg	Gentamicin, streptomycin, ampicillin, ciprofloxacin (adapted rugose); sulphamethoxazole/trimethoprim and streptomycin (adapted smoothly)	Not reported	[24]
Chlorine	*E. coli*	Trimethoprim	Not reported	[25]
Chlorine (>1.0 mg Cl2/L)	*E. coli*	Tetracycline	Not reported	[26]
Chlorine (2 mg/L)	*E. coli*	Ampicillin	Not reported	[27]
Chlorine (1 and 5 mg/L)	*K. pneumoniae*	Ampicillin	Not reported	[28]
Chlorine (4 and 8 mg/L)	*P. aeruginosa*	Ceftazidime, chloramphenicol, ampicillin	Not reported	[29]
Chlorine	*P. aeruginosa*	Amikacin, gentamicin	Not reported	[21]
Heavy Metals				

Non-Antibiotic Antimicrobials	Bacterial Species	Antibiotics to which Susceptibility was Decreased	Bacterial Adaptation/Mechanism of Resistance	Reference
Agrochemicals				
Cr Pb Cd Zn Cu	*E. coli*	Fluoroquinolone Vancomycin Quinolone Fluoroquinolone, ampicillin, cephalothin, and trimethoprim/sulfamethoxazole, vancomycin Ampicillin, cephalothin, trimethoprim/sulfamethoxazole	Not reported	
Hg	Enterobacteriaceae	Various antibiotics (not specified)	Not reported	
Co, Cr, Cu, Hg, Ni, Zn Pb	*Salmonella* spp.	Penicillin Ampicillin, chloramphenicol, tetracycline		[30]
Ag, Cd, Cu, Ni, Pb, Zn Zn, Cu	*P. aeruginosa*	Aminoglycoside, amphenicol, macrolide, nitrofuran, penicillin, Quinolone, sulfonamide, tetracycline, trimethoprim/sulfamethoxazole; imipenem	Outer membrane proteins Co-regulation	
Cd	*A. baumannii,* *Klebsiella* spp., *P. aeruginosa,* *Providencia* spp, *Proteus* spp.	Penicillin, ampicillin	Not reported	
Hg	*E. coli,* *Klebsiella* spp., *Shigella* spp.	Tetracycline, Sulfamethoxazole/trimethoprim	Not reported	
Cu, Ni, Zn	*Klebsiella* spp., *P. aeruginosa,* *Proteus* spp.	Ampicillin, amoxicillin, tetracycline	Not reported	
Food preservatives and decontaminants				
Lactic acid	*Cronobacter sakazakii*	Neomycin, tetracycline, tilmicosin, florfenicol, Amoxicillin, ampicillin, vancomycin, ciprofloxacin, enrofloxacin	Not reported	[31]
Acidification with HCl	*E. coli* *S.* Typhimurium *S. aureus*	Amikacin, ceftriaxone, nalidixic acid Amikacin, ceftriaxone, trimethoprim Gentamicin, erythromycin	Not reported	[32]
Acetic acid, sodium benzoate, sodium nitrite	*S.* Enteritidis	Tetracycline	*mar* mutation	[23]
Trisodium phosphate		Ampicillin	Not reported	
Sodium nitrite	*E. coli*	Spectinomycin, amikacin, kanamycin, streptomycin, cefazolin, cephalothin, cefotaxime, ceftazidime, cefepime, aztreonam, nalidixic acid, enrofloxacin, phosphomycin, nitrofurantoin	Increase in cell surface hydrophobicity and biofilm formation	[14]
Lactic acid (pH 6, 5.5, 5)	*L. monocytogenes*	Streptomycin, gentamicin, ampicillin, penicillin, ciprofloxacin, enrofloxacin	Not reported	[33]
Lactic acid (1%, pH 3.5)	*L. monocytogenes*	Ciprofloxacin, nitrofurantoin, erythromycin	Not reported	[34]
Sulphuric acid (pH 3, 5, 6)	*Acinetobacter baumannii*	Amikacin, piperacillin, tazobactam, imipenem, meropenem	Not reported	[35]

Non-Antibiotic Antimicrobials	Bacterial Species	Antibiotics to which Susceptibility was Decreased	Bacterial Adaptation/Mechanism of Resistance	Reference
Agrochemicals				
Natural Compounds				
Epigallocathechin gallate	***S. epidermis, S. aureus***	**Vancomycin, oxacillin, ampicillin**	**Increased cell wall thickness, with a role of the two-component VraSR system**	**[36,37]**
	E. coli	**Gentamicin, erythromycin, vancomycin, chloramphenicol, tetracycline, trimethoprim, mupirocin**		
***Melaleuca alternifolia* oil**	***S.* Enteritidis, *S.* Typhimurium**	**Gentamicin, chloramphenicol, tetracycline, streptomycin, trimethoprim, mupirocin**	**Not reported**	**[38]**
	S. aureus	**Gentamicin, vancomycin, chloramphenicol, trimethoprim, ampicillin, fusidic acid, mupirocin**		
***Thymus marroccanus* essential oil**	***E. coli***	**Chloramphenicol, nalidixic acid, tetracycline, erythromycin**	**Overexpression of AcrAB-tolC and decrease of the expression of outer membrane proteins**	**[39]**
Pine oil	***E. coli***	**Tetracycline, ampicillin, chloramphenicol**	**Overexpression of marA gene.**	**[40]**

variants were exposed to sub-MIC of QACs or triclosan, a reduction in outer membrane porins and increase in the expression of the AcrAB-TolC efflux pump occurred. Further, benzalkonium chloride (classified as a QACs) could trigger the expression levels of MdrL efflux pump in Listeria monocytogenes (L. monocytogenes), leading to a decrease in the susceptibility to ciprofloxacin by increasing two-fold the MIC value, or even changing the profile from susceptible to resistant to various strains for cefotaxime and cephalothin [7][19]. In P. aeruginosa, the exposure to sub-MIC levels of benzalkonium chloride and chlorhexidine could decrease the expression of the repressor gene mexR and, in turn, induce the expression of MexAB-OprM and MexCD-OprJ efflux pumps [20][21]. In fact, the exposure to sub-inhibitory concentrations of benzalkonium chloride caused a change in the categorization of P. aeruginosa, from ciprofloxacin-susceptible to -resistant [20].

Additionally, some oxidizer components, such as hydrogen peroxide and hypochlorous acid, which are used widely in the poultry industry at present, can trigger oxyR radical defense or soxRS systems in bacteria. These activations might lead to an overexpression of efflux pumps that render resistance to streptomycin and rifampin [17].

Chlorine is one of the most widely used disinfection methods, mainly due to its low cost and durability. By applying chlorine to bacteria, the first attack is directed towards proteins and peptidoglycan. After this, it can enter cells primarily through diffusion and transport, penetrate the cell wall and reach the cytoplasm, and then react with cellular components and coagulate enzymes and nucleic acids, causing microbial death [22].

As found for other compounds, the adaptation of bacteria to chlorine could constitute a potential threat to food safety by inducing cross-protection to clinically important antibiotics, as well as by contributing to the spread of resistance to other bacteria [23][24]. The exposure to 25 ppm of chlorine induced the marRAB operon, suggesting that mar mutation was responsible for these higher resistances, as a global regulator controlling intrinsic resistance towards structurally and functionally unrelated antibiotics and associated with an increased expression of efflux pumps [25]. (2016) observed different effects of chlorine treatment (at both 1 and 5 mg/L) on the antibiotic resistance profile in residual K. pneumoniae strains, namely, an increase in resistance to ampicillin as well as an increase in susceptibility to cefaclor and tetracycline were reported [26]. (2019) investigated the chlorine injury in P. aeruginosa at different exposure levels, and only strains with final chlorine concentrations of 4 and 8 mg enhanced antibiotic resistance against ceftazidime, chloramphenicol and ampicillin, similarly to MIC values reported by Nasr et al.

(2020) found that E. coli, Salmonella Aberdeen, P. aeruginosa and Enterococcus faecalis (E. faecalis) showed diverse resistance to sodium hypochlorite and chlorine disinfection naturally accelerated the genetic exchange in or across bacterial genera by promoting the horizontal transfer of plasmids by natural transformation. (2018) showed that both triclosan (0.1 mg/L) and chlorhexidine (24.4 µg/L) can promote the horizontal transfer of antibiotic resistance [27]. (2017) observed similar results and proposed that the sub-MIC of chlorine, chloramine and hydrogen peroxide could promote ARG transfer between E. coli strains, as well as from E. coli to S. Typhimurium, by an average of one to five-fold. Therefore, a strategy to correctly use these chemicals according to their effect on antibiotic resistance or replace them by applying other techniques, should be defined.

Once in the environment, their persistence, as well as their bioaccumulation in the food chain, have long-term impacts, both posing food safety issues and acting as a selective pressure for adaptations in microbial communities, even considering that heavy metals are more stable and resistant to degradation than antibiotics [28]. In addition, on one hand, the alteration in the metal/antibiotic target is associated with copper, mercury, zinc, ciprofloxacin, rifampicin, β-lactams, and trimethoprim, and on the other, the maintenance of multi-resistance is performed by plasmids harboring antibiotic resistance genes, as well as genes encoding resistance to heavy metal, for example, conjugative plasmids for the co-transfer of macrolide and glycopeptide copper resistance, or for genes encoding β-lactamases (blaCTX-M) or even bla, strAB, catI, sulII and dhfr1b genes for multiple resistance to ampicillin, streptomycin, chloramphenicol, sulphonamide and trimethoprim, as well as the linkage of copper, silver and mercury-resistance operons. (2019) reviewed the association between ten heavy metals (cadmium, copper, zinc, mercury, cobalt, chromium, nickel, silver, iron, and arsenic) and antibiotic resistance versus different antibiotic classes within human pathogenic bacteria (P. aeruginosa, E. coli, (2020) considered the presence of co-resistance to metals and antibiotics in aquatic environments worldwide and stated that, even in environments where antibiotics have never been used, the presence of heavy metals is sufficient to select for antibiotic-resistant bacteria and antibiotic resistance genes.

Antimicrobials are widely used throughout the food chain, whether in the agriculture and livestock industry or directly in foods, with the direct or indirect potential to affect the development of antimicrobial resistance by bacteria dispersal along the farm-to -fork continuum. While the adaptation to antibiotics and biocides has been widely studied, the response and adaptation of foodborne bacteria to food preservatives and decontaminants is poorly studied (Table 1.).

Acids are included in the compounds more vastly used in food preservation and decontamination procedures. Acidic stress is as a primary barrier in food and, therefore, the adaptive responses of foodborne pathogens may enhance resistance to other substances and could lead to cross-protection. When exposed to acid stress, microorganisms may adapt to these environments by the overexpression of sigma factor, synthesis of outer membrane proteins, by alteration of the membrane permeability and of the cell membrane fluidity by modifying the membrane lipid composition. These changes have a direct effect on the influx and efflux of antibiotics across the cell membrane and thus on the antibiotic susceptibility of the bacterial cell itself [29].

is a crucial foodborne pathogen faced with different stress conditions, both in their environmental niches, mainly during the production and storage of foodstuff, as well as in the defensive barriers (gastrointestinal tract) of their hosts. Four wild-type strains of S. Typhimurium, E. coli, and S. aureus, under conditions of low-pH stress of 5.0, 4.5, or 4.0 obtained by acidification with HCl, significantly altered their antibiotic resistance levels, with the higher MIC of amikacin, ceftriaxone and nalidixic acid than controls. This decreased susceptibility was maintained after the stress was removed in E. coli and S. aureus, but not in S. Typhimurium, suggesting that the observed increase in MICs could be a stress response involving the whole population or the selection and outgrowth of a subpopulation of hyper-resistant clones [30]. (2010) found no association between antibiotic resistance and acid stress response for Salmonella spp.

Even in L. monocytogenes, which is a versatile organism with the ability to survive for long periods under adverse environmental conditions including cold storage, high NaCl concentrations and acidic pH, some adaptive responses were evidenced. The results demonstrated that food strains resistant to ciprofloxacin, nitrofurantoin and erythromycin were significantly more resistant to acidic stress than susceptible strains [31]. (2018) tested the influence of pH stress (acid at 3, 5, and 6 and alkaline at 9 and 10 pH (2011) and was shown to increase sensitivity toward streptomycin, gentamicin, kanamycin and doxycycline, while augmenting resistance to tetracycline, tilmicosin, florfenicol, amoxicillin, ampicillin, vancomycin and enrofloxacin (with variable strain response toward ciprofloxacin).

Considering the diverse results obtained and a practical application of acidic stress in food processing, the use of lactic and acetic acids for decontamination of food products was recently addressed in a scientific opinion on the evaluation of the safety and efficacy of these acids on the reduction in microbiological surface contamination on pork carcasses and pork cuts, conducted by the European Food Safety Authority Panel on Food Contact Materials, Enzymes and Processing Aids by request of the European Commission. This report considered several points, namely the potential selection and

emergence of bacteria with reduced susceptibility to biocides and/or resistance to antibiotics with therapeutic use. The existence of insufficient indications that could support the hypothesis that a sublethal exposure of bacteria to organic acids may promote or augment antibiotic or biocide resistance was pointed out [32]. Despite the fact that a possible acid adaptation may occur, leading to a reduced efficacy of organic acids or other chemical treatments [33][34] (and reviewed by [35]), or even to a small decrease in susceptibility to some antibiotics [25][30], their impact on public health is unknown [32].

(2006) explored the potential of widely used food preservatives to confer antibiotic resistance to Salmonella Enteritidis, showing that a single exposure to acetic acid, sodium benzoate, or sodium nitrite can result in a stable decrease in susceptibility to tetracycline. (2015) studied the adaptation and cross-adaptation of E. coli ATCC 12806 by passage through gradually higher concentrations of trisodium phosphate, sodium nitrite, and sodium hypochlorite, observing an adaptative tolerance to these compounds. This adaptation was stable for sodium nitrite and sodium hypochlorite and could be at least partially caused by efflux pumps and changes in cell surface hydrophobicity [36]. In addition, the adaptation to sodium nitrite and sodium hypochlorite substantially improved biofilm formation ability.

On the other hand, strains adapted to QACs, hexachlorophene [2, 2′-methylenebis (3, 4, 6-trichlorophenol)] or chlorhexidine presented a generalized increase in the susceptibility to preservatives, with some exceptions, which may be strain-dependent [37]. A correlation between antibiotic resistance and an increased tolerance to stress was described for drug- or multidrug-resistant S. aureus strains or antibiotic-adapted S. Typhimurium. A similar relation was established for various Salmonella serotypes, where a correlation between survival to acidified sodium chloride and trisodium phosphate was presented. The significance of the correlation was more evident for acidified sodium chloride.

Similar to other stressors, antibiotic resistance could be additionally potentiated in an indirect form by environmental stresses, such as the ones found in food preservation systems, such as high/low temperature, pH and osmotic stresses, which may increase the rates of horizontal transmission of plasmids between E. coli strains or E. coli and S. Typhimurium, stimulating the antibiotic resistance exchange. Thus, the use of sublethal food preservation systems may contribute to the dissemination of antibiotic resistance [38]. For example, the rate of horizontal transmission of antibiotic resistance plasmids among E. coli strains and between E. coli and S. Typhimurium was investigated by McMahon et al. (2007), showing an increased rate of horizontal transmission of plasmids R386 and TP307 when a prestressed donor and recipient cells are mated under sublethal acid stress [38].

A growing interest in natural compounds as an alternative to chemical disinfectants and food preservatives was reported, focused on their safety and ability to act in multiple-cell targets, thus potentially limiting the development of resistance [39]. Furthermore, to reduce the use of agrochemicals, plant extracts were used as biopesticides, with some already-commercialized organic pesticides based on essential oils (reviewed by Durán-Lara et al. This phenomenon has been observed for several antimicrobials, and some studies have shown that the exposure of bacteria to sub-inhibitory concentrations of natural compounds may lead to the cross-resistance to antibiotics or even food-associated stresses, while others have pointed out that the use of natural compounds would not influence the resistance to antibiotics. Considering this, when evaluating the antimicrobial potential of natural compounds as food preservatives or for application in several stages of the food chain, the possible facilitation of the emergence of AMR by microbial exposure should be assessed.

For example, epigallocathechin gallate (EGCG), a major polyphenolic component of green tea extract, is known to possess many beneficial properties, including antibacterial activity. Furthermore, it was associated with an induction of a cell wall stress response in S. aureus, modulated by the two-component VraSR system, in the same manner as cell-wall-active antibiotics [40]. The upregulation of genes encoding efflux system proteins by the exposure of Pseudomonas fluorescens, a spoilage bacterium commonly found in diverse food matrixes, to EGCG, has been described. Efflux is one of the mechanisms commonly associated with cross-resistance to compounds without a chemical relation, and even the selection or acquisition of other resistance mechanisms [41], which point to a possible cross-resistance with antibiotics and the facilitation of AMR emergence.

The cross-adaptation induced by other natural products has been studied; this is the case of the tea tree oil (Melaleuca alternifolia), an essential oil which is widely available and vastly investigated as an alternative antimicrobial, anti-inflammatory and anti-cancer agent for topical use, since it is toxic if ingested in high doses [42][43]. Further, after the adaptation of staphylococci strains to tea tree oil, a reduction in the susceptibility to mupirocin, fusidic acid, chloramphenicol, linezolid, and vancomycin was observed, although this was a transient, decreased susceptibility [44]. Another study focusing on a similar analysis reported that exposure to tea tree oil did not present any global effects on the development of antibiotic resistance in S. aureus, S. epidermidis, and E. coli, and that the repeated exposure to its main

component, terpinen-4-ol, did not lead to a decrease in susceptibility. In fact, the authors suggest that, if an adaptive response was induced, it would not alter the antimicrobial susceptibility or conferred cross-protection to other antimicrobial agents [42].

The authors explored the membrane-associated mechanisms of resistance and observed an overexpression of an efflux pump immunorelated to AcrAB-tolC and a decrease in the expression of outer membrane proteins in adapted strains [45]. A diminution in the susceptibility of Serratia marcescens to antibiotics was also found after 50 sequential passages with a sub-inhibitory concentration of oregano essential oil, while the same was not observed for cinnamon essential oil or other bacteria, such as Proteus mirabilis, P. aeruginosa, or Morganella morganii [46]. The exposure of S. Enteritidis to trans-cinnamaldehyde and eugenol induced the upregulation of multiple antibiotic resistance (mar) locus genes by both compounds, and of efflux pump genes acrAB by eugenol, while the compounds downregulated the expression of outer membrane proteins [47]. The strains' adaptation to natural compounds by the regulation of efflux pumps, and outer membrane proteins can be associated with an increased resistance to antibiotics, as antibiotic resistance also relies on these mechanisms.

Some antimicrobial peptides are currently used as food preservatives, such as nisin and related compounds such as pediocin, which are secreted by lactic acid bacteria [48]. Nisin is a natural antimicrobial agent, which has been widely studied for food applications, namely, as a dairy preservative. It is Generally Recognized as Safe (GRAS) by the U.S. Food and Drug administration and suggested for use as an antimicrobial agent to inhibit the outgrowth of Clostridium botulinum spores and toxin formation in pasteurized cheese spreads [49][50]. In fact, nisin-resistant E. faecalis strains were less susceptible to various antibiotics, and a decrease in susceptibility to antibiotics was observed with the gradual reduction in nisin susceptibility [51].

Beyond antibiotic resistance, bacterial adaptation to natural compounds may also lead to increased resistance to commonly used biocides. In fact, a study characterizing the adaptation of S. Typhimurium to sublethal concentrations of thymol, carvacrol, citral, and eugenol, showed increased cell resistance to the bactericidal activity of peracetic acid and didecyl dimethyl ammonium bromide [52].

Although several works reported a cross-adaptation with natural compounds, other studies reported, that the continuous mode of use of eugenol and citral would not pose a risk of resistance for S. aureus or L. monocytogenes [53]. A similar behavior was observed for resveratrol [54]. Additionally, a short incubation with sub-inhibitory concentrations of thymoquinone, the main, biologically active component of the volatile oil of Nigella sativa seeds, increased the susceptibility of C. sakazakii to ampicillin and cefoxitin [55]. A similar trend was observed for multidrug-resistant S. enterica isolates from human outbreaks or from poultry origin, for which no direct-tolerance or cross-tolerance to ciprofloxacin were induced after habituation in sub-inhibitory concentrations of Origanum vulgare L. essential oil (½ or ¼ MIC for 24, 48, and 72 h) [56].

3. Physical Methods of Food Processing That May Influence Antibiotic Susceptibility

Throughout the food chain, bacteria are continually exposed to several factors, strategies and treatments that determine various chemical (acids, chlorine) and physical (heat, pressure and radiation) stresses, from primary production to food processing and preservation, as well as at-home preparation. As was clearly described in the study of Liao et al. (2020), the interplay of antibiotic resistance and stress tolerance of bacteria is crucial from a food safety perspective, because various food-processing technologies can sharpen the resistance of pathogenic bacteria in foods to a range of currently used antibiotics, and vice versa, which poses a potential risk to food safety and human health [7]. Following this, a comprehensive evaluation of the cross-resistance phenomenon associated with physical treatments was performed.

In contrast, an adaptation to environmental heat stress (at 45 °C for 2 h) of one strain of L. monocytogenes with increased resistance to trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, penicillin, ampicillin, gentamicin, and rifampicin was reported, with a from two- to four-fold increase in the MIC. The authors concluded that, in L. monocytogenes, the stress responses to heat shock induced stress proteins [57]. The higher resistance exhibited is suggested to be due to alterations in the expression of porin channels, the induction of efflux pump expression, or to the expression and synthesis of stress proteins, especially sigma factors (RpoS and SigB, respectively, for Gram-positive and Gram-negative bacteria), which could be responsible for the reduction in susceptibility to a majority of the antibiotics. Moreover, an increased resistance of five strains of C. sakazakii to broad-spectrum antibiotics (streptomycin, gentamicin, kanamycin, neomycin, tetracycline, doxycycline, tilmicosin, florfenicol, ampicillin, amoxicillin, vancomycin, ciprofloxacin, and enrofloxacin) was reported under heat stress (55 °C for 5 min) by Al-Nabulsi et al.

However, it should be mentioned that all the above-mentioned studies consider thermal stresses that could not be absolutely compared with the heat treatments routinely used in the food industry. For example, in the dairy industry, pasteurization and sterilization by Ultra-High Temperature (UHT) are thermal treatments of uncontested interest. (2020) investigated the presence of 1 genomic and 9 plasmid-mediated AMR genes in commercial pasteurized and UHT milk samples; a high prevalence of sul2 (67.9 and 42.6%), tetA (54.8 and 27.9%), tetM (31 and 26.5%), and blaTEM-1B (42.9 and 32.4%) was, respectively, detected in pasteurized and UHT milk, while mecA was not detected. This study resulted from a concern associated with the inability of pasteurization to destruct plasmid-mediated AMR genes and their possible horizontal transfer from pasteurized milk [58].

Ultraviolet (UV) radiation uses physical energy, and it is a non-thermal and non-chemical technology used by the food industry for liquid and solid surface decontamination, to control foodborne pathogens and spoilage microorganisms, as well as viruses and protozoa. However, the repair mechanism of UV damage, especially by photoreactivation, is a major disadvantage of UV disinfection [59]. The germicidal effects of UV radiation mainly depend on the UV dose (J/m2) [60] and the removal effect of UV on various ARBs, even if selective, was much stronger than that of ARGs [61]. The commonly used dosages of UV do not guarantee the complete inactivation of ARGs, for which an effective removal occurs at a much higher UV fluence (>100 to extreme values of 200−400 mJ/cm2), for damaging DNA to avoid transformation [62][61][63].

In the literature, microbial exposure to other common stresses belonging to decontamination and sanitation strategies is scarce, and the results of susceptibility to different antimicrobials in several foodborne pathogens, exposed to UV treatments, were affected by the investigated microorganism, the target antibiotic, the UV exposure and the contact time. (2017), a selective change in the inhibition zone diameters of surviving antibiotic-resistant E. coli and slight damage to ARGs were reported after UV exposure at 80 mJ/cm2. The genomic background of the strains seems to be important for the emergence of the variant strains: L. monocytogenes displayed several variants whereas, for other strains, it was not possible to identify AMR variants. Mechanistically, UV exposure caused oxidative stress in P. aeruginosa, inducing the dysregulation of genes, and contributing to the related antibiotic resistance genes, involving an elevated expression of the mexC gene, which encodes a protein of the MexCD-OprJ pump, which functions as a determinant of antimicrobial resistance to several clinical antimicrobials, such as ciprofloxacin and tetracycline, but not, for example, polymyxin B.

In general, UV irradiation inactivates several ARBs and the selectivity of UV disinfection to ARB and ARGs might lead to an increase in specific ARB ratios [61][63]. In addition, tetracycline-resistant bacteria showed more tolerance to low UV fluence, owing to the fact that UV treatment has selectivity for bacterial antibiotic resistance [64]. In another study, UV radiation affected E. coli strains resistant to ciprofloxacin, but no changes to amoxicillin and sulfamethoxazole were observed, as well as no effective control of ARB spread [65]. AOPs seems to be more promising in terms of both the inactivation of resistant bacteria and their genetic material compared to conventional disinfection methods, such as chlorination or UV-C radiation, due to the superior oxidative effects of free radicals not only on nucleic acids but also in other biomolecules [66], even if there are still crucial gaps to be filled regarding the potential spread of AMR [62], and in antibiotic fermentation residues [67].

Plasma technology belongs to AOP and is based on the ionization of a carrier gas through the application of electric discharges at atmospheric pressure and room temperature, with the consequent generation of electrons, ions, UV photons, charged particles, and free radicals (including reactive oxygen and nitrogen species), which cause direct effects that damage microbial cell membranes, DNA, and proteins [68]. (2018) found that the sublethal treatment of gas plasma decreased the MICs of MRSA against tetracycline, gentamicin, clindamycin, chloramphenicol, ciprofloxacin, rifampicin, and vancomycin and increased persisters eradication, along with increases in the levels of reactive oxygen species and reactive nitrogen species in MRSA cells [69]. and L. monocytogenes strains repeatedly exposed to sublethal non-thermal atmospheric plasma, accompanied by a gradual decrease in bacterial susceptibility in the investigated strains. In addition, the mapping of the genome of S. Typhimurium and the variant versus ciprofloxacin and streptomycin evidenced a common evolution for various generations, followed by a parallel divergent evolution, which gave rise to relevant phenotype shifts, with different genes harboring non-synonymous mutations in the resistant variants [68].

4. Influence of Bacteriophage Application on Antibiotic Susceptibility

Bacteriophage (phage) are the most abundant types of life on earth. They are completely dependent on their host for activity; therefore, they could be one of the most relevant biological stressors for bacteria, namely for foodborne bacteria [70][71][72].

They are known to treat infections in humans and animals or even to be used in packaged foods, as an alternative to antimicrobial components [73]. The application of phage has been supported by its advantages, such as its presenting fewer adverse effects on commensal microbiota, being harmless to farm animals and humans, and its interesting

effectiveness against antibiotic-resistant bacteria. The proper application of phage in the food chain, from farm to fork, can be considered as a replacement or complement of the use of antibiotics and pesticides. However, based on expert opinions, the route of administration, dosage, and type of phages are very important for the outcome of phage therapy.

Phage may act on resistant bacteria or work synergistically with antibiotics; moreover, phage selection may also result in bacteria developing phage-resistance, simultaneously increasing susceptibility to antibiotics (trade-off) or leading to modifications associated with cross-resistance to antibiotics [70][74][75].

In some studies, phage presented a trade-up on bacteria, and their use led to resistance against the same and other phages strains, as well as to antibiotics, due to the cross-resistance phenomenon. Reversely, the application of some antibiotics could also induce bacteria to resistance against phage. In contrast, other authors observed the trade-off between phage species and antibiotics and proposed an increased sensitivity to antibiotics under the influence of phage [70][75][76]. The authors showed that emerging resistance against one factor did not affect the emergence of resistance in another, with susceptibility to phages and antibiotics evolving independently [77].

When a bacterium encounters a phage, it tries to survive by several known mechanisms, with some of them being able to influence the efficacy of antibiotics and confer resistance to them. Another important mechanism, which is involved in the antibiotic resistance induced by phage, is the transfer of ARGs between bacteria via transduction [77][78]. Another study showed that Klebsiella phages can lead to the overexpression of some genes in this bacterium, including aac(6′)-Ib-cr, which is responsible for aminoglycoside and quinolone resistance, and the vagC gene, which increases β-lactamase activity. Another investigation suggested that resistance against T6 phage infection in E. coli can induce cross-resistance against gentamicin, as tsx gene deletion, a gene that encodes the nucleotide channel used as a receptor by the phage, confers resistance to the phage and simultaneously increases resistance to gentamicin [77].

The modification of LPS, possibly due to the stress pressures of phages infection or β-lactams exposure, changes the structure of porin (OmpF)-LPS complexes. Alterations in those structures contributes to resistance against phage or antibiotics. Therefore, resistance to one of them may fortuitously confer cross-resistance to the other one [70]. Conversely, T3 phage-resistant mutants can be developed following exposure to a sublethal dose of amoxicillin [70].

(2020) also showed that the long-term exposure to phage OMKO1 can decrease the MIC level of antibiotic resistance in more than 60% for P. aeruginosa (Washington PAO1) against tetracycline, erythromycin, and ciprofloxacin by the reduction in efflux pump efficiency [79]. Supporting this, E. coli TLS phage-resistant mutants suffer a change in the AcrAB-TolC system that might pleiotropically lead to a loss of antibiotic resistance [74][80]. U136B phage also uses TolC as a receptor to infect E. coli, which was related to a trade-off between phage resistance and antibiotic resistance, with tolC mutants associated with phage-resistance being more sensitive to tetracycline and colistin in comparison to their parental strains. Meanwhile, a subset of the other phage-resistant mutants with LPS-related mutations showed decreased resistance to colistin, while presenting increased resistance to tetracycline, which indicates the variability in phage-antibiotic resistance interaction in bacteria [74][79].

In sum, increasing knowledge of the interaction between bacteria and phage is necessary to evaluate phage application in the food chain and reduce the cross-resistance phenomena between antibiotics and phages. By accurately identifying candidate phages in each foodborne bacterium, with both trade-off and synergistic effects with a class of antibiotics, a therapeutic combination of both types of antibacterial agent can be developed against MDR bacteria. However, despite the progress in the understanding of associations between antibiotics and phage in natural environments, animal farms, and clinical populations, we still have little information in this regard. Therefore, in any phage therapy protocol and study, particular attention should be paid to cross-resistance, unexpected pleiotropy, and community evolution.

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