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Antimicrobial Resistance along the Food Chain: Contaminated and Industrially Processed Nutrients

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Abstract

The presence of antibiotics-resistant microorganisms became a universal challenge to prevent and treat human disease propagation through zoonotic, food components and industrial processed food transmissions. The rising prevalence of morbidity and mortality associated with over and inappropriate use of antibiotics induced global efforts to anticipate this worldwide health security threat. Much of the theme is centered along the food chain, starting with the microbial and antibiotics contaminated environment, misusage of antibiotics in agricultural farms and plantations, through hospitals and clinics. The present narrative review updates on the antibiotic resistance gene transfer in ready to use industrial nutrients and in contaminated food products. A more promising and hopefully rewarding aspect, in the current review, expands on the natural antimicrobial components that contribute to the suppression of antibacterial resistance in various types of microorganisms. Food transferred bacterial antibiotic resistance should be taken in account in the national and international efforts to anticipate this global health security threat.

Keywords: Antimicrobial Resistance; Antibiotics Resistance Gene; Food Chain; Antimicrobial Activity; Horizontal Gene Transfer; Multidrug Resistance; Mobile Genetic Elements; Bacteria; Microbe; Food

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Introduction

Antibiotics are present since their early medical introduction in the 1940s. For more than the last 8 decades, their consumption and often their inappropriate use have substantially increased. It is estimated that antibiotic resistance kills around 23,000 people per year with an economic burden over $20 billion in additional expenses, in the United States [1]. The rising prevalence in morbidity and mortality associated with over and inappropriate use of antibiotics provoked national and international steps to anticipate this global health security threat.

The use and misuse of antimicrobials in sectors related to the surrounding environment, animals, as well as humans contributes to the distribution of hostile and therapy-resistant bacteria. The wide distribution of resistant microbes, plasmid and other mobile components within and between these environments and globally is a vital aspect that should be addressed [2]. Some typical examples are the extensive medication of animals, along with critically important antibiotics, such as cephalosporins and fluoroquinolones, for humans, and the over use of antibacterial, such as colistin, tetracyclines and macrolides, added to the food of farm animals for growth promotion [3].

The composition of ecological-trophic and pollutant-resistant groups of microbial associations and molecular-genetic properties of microorganisms under conditions of complex pollution were extensively reviewed [2,4]. Wide presence of resistance and residual antimicrobials occurring in water, air, soil, industrial, agricultural, wildlife and numerous other ecological niches. Intriguingly, pharmaceutical, industrial, agricultural and hospital waste and manure originate from farms harboring resistant microbes, containing resistance mobile genes, for a long time [2,5, and 6]. Interestingly, the plant's domain is protected from a broad range of toxic biotic agents by sensitive perception events, various signal transduction cascades, and their very efficient capacity to elicit defensive mechanisms [6-8].

It is established that the occurrence of multi-resistance in microorganisms is impacted by a significant environmental and anthropogenic influences [2,9]. Infections associated with the provision of ready-to-eat foods and cooked food are becoming more and more relevant [10,11]. It appears that the main source of antibiotic-resistance is non-compliance with safety regulations during the cooking process, resulting in development and distribution of microorganisms in the final product [12,13]. Those processes are influenced by environmental factors such as: fecal pollution, poor hygiene habits, noticeable chemicals, phenolics and petroleum and the above accepted background of a number of heavy metals. It strongly depends not only on direct household and industrial pollutants, but also on the methods of preparation, storage and transportation of the final products [2,3,

and 12-14]. Microbial analysis revealed that the product is subjected to a strong anthropogenic impact, since a high percentage of microbes, as well as resistant intestinal bacteria, including pathogenic ones, were found in the processed products, mainly in individual that are nearby farms located [2,5, and 14]. Moreover, uncontrolled use of antibacterial drugs in doses exceeding the permissible ones and the use of excessive disinfection methods, increases the prevalence of multi-resistance in microorganisms. Thus, resulting in the difficulties of diagnosis, treatment and medical care offered to people, leading to severe morbidity and enhanced number of complications [2,9, and 11].

Preventive measures must include efforts to follow the instructions of the regulatory authorities who should continuously judge the effectiveness of existing antimicrobials [2,9]. More effective acts to suppress this problem includes taking steps such as limiting the spreading of contamination and infection and by trying to decrease the inappropriate usage of antibiotics, when used in high volumes, in farming [4,6], hospitals, and aquaculture environments [2,3]. Furthermore, most of antimicrobial's classes used to treat human microbial infections are also shared in animals [6,7], thus, it is possible to maintain the effectiveness of their use in human medicine, by reducing their usage in animals.

The joint effort of multiple physicians with scientific teams to obtain optimal health for human beings, wildlife and domestic animals, plants, and the surrounding environment is the One Public Health Perspective [2]. Many national and several international agencies have adopted a One Health approach within their action plans to change their attitude for antimicrobial resistance [2,3, and 6]. New guidelines were recently launched by the WHO for the use of wide spread antimicrobials in food-producing farms, recommending that farmers and the food industry, stop using antimicrobials routinely to enhance growth and suppress potential disease in healthy animals [1,2, and 4].

Given the size of the problem of the antibiotics resistance genes (ARG) world-wide dispersion, the present review updates on antibiotic resistance, concentrating on the food chain and more specifically, on the contaminated and industrial processed nutrient's delivery of those harmful genes. Figure 1 represent a schematic summary of antimicrobial resistance along the food chain transmitted by contaminated and processed nutrients. The data will be presented in two aspects: ARG transfer in ready to use nutrients and in contaminated food products. The last section summarized the natural antimicrobial components that contribute to the suppression of antibacterial resistance of numerous types of microorganisms.

ARG Transfer in Ready to use Food

The topic of ready-to-eat products and antibiotics gene transfer is summarized in table 1. The acquisition of antimicrobial resistance in microorganisms largely determines the effectiveness and outcome of various veterinary measures [15]. Exploration of antibiotic resistance, monitoring of herds and properly developed treatment regimens are measures that will help reduce the risk of the distribution of pathogenic and opportunistic microorganisms. The dimension of the problem is illustrated by the fact that 67.1 % of the isolates expressed resistance to one or more antibiotics [16]. The largest number of strains were resistant to novobiocin (49.7 %), while the smallest - to vancomycin (2.6 %). It should be noted that there is antibiotic resistance to the new generation drugs like novobiocin and vancomycin, which are widely used in modern medicine. The most studied antibiotics were gentamicin (81.9 %), rifampicin (86.5%) and vancomycin (97.4%) [2,16]. The tendency to develop polyresistance raises another concern. In fact, 55.6-61.5 % of polyresistant strains after antibiotic therapy versus 33.3-43.8 % before treatment by antibiotics, illustrates the huge dimension of the problem [2,4,10, and 13]. Analyzing food samples for microbial communities and the ARGs formed under the influence of anthropogenic transformation of the environment are presented in table 1. Quantitative data on the prevalence of coliform bacteria and their resistance to antibiotics represent an additional example for this difficult and worrying global problem [17].

Other mobile genetic elements (MGEs) conferring antibiotics and heavy metal ions resistance, allowing survival under substantial anti-bacterial selective pressures, are well described. In fact, positive selection acts on the microbial genome via point mutation and/or genetic recombination causing allelic variation and loss or gain of gene function. As a result, metabolic modifications occur, in response to those expressed virulence-related genes that reside in a plethora of commonly consumed nutrients [15-17, 31-33].

The universal phenomenon of AGR suggests that the environmental proximity between human-driven domestication and close reciprocity with livestock, created many successful host-switch events between livestock hosts and human beings [34]. More so, industrialization of agriculture and extensive use of veterinary food supplements containing antibiotics in intensive farming have enhanced the evolution of resistant microorganisms' populations. Those processes directly drove the emergence of resistance against distinct antibiotics in hospital, clinics and agriculture [34]. This reality supports the idea that regulations and strike surveillance could represent a critical game changer in early detection of emerging clones that were transferred in between or crossed hosts.

Taken together, the current knowledge provides a clear-cut and comprehensive view of a model for multi-creature pathobionts to undergo abrupt modification in biological diverse ecology by genetic adaptation. Exploring the functional basis of those genetic alterations will unravel key host-pathogen cross-talks that could lead to new therapeutic strategies. As an example, identifying frequently used routes for *S. aureus* livestock-human host-species switches and distinct types of antimicrobial resistance in humans and livestock animals could induce a plan for a more cost-effective farm secure surveillance and highly controlled antimicrobial practices to prevent the evolution of novel resistant clones [5,32, and 34]. The findings can apply to many other frequent pathobionts able to disseminate between animals and mankind.

As a demonstrative example, done in a well surveyed area, the number of coliforms that were found were rather high, ranging between one to several thousand CFU per 100 ml [4]. It was shown that the number of both total and fecal coliform bacteria in a settling pond, is significantly higher after compared to before the facilities' treatments. Thus, the content of sanitary-indicative microorganisms does not correspond to hygienic standards. Interestingly, when the number of isolates with multidrug-resistance (MDR) and extreme resistance was counted, the cultures with multiple drug resistance in summer were less common than in autumn (60% and 73.6%, respectively) [18,30]. Of note, in the area of treated food release, there was an increased number of microorganisms with MDR. The antibiotics with the greatest capacity to induce MDR were cotrimoxazole, ofloxacin, chloramphenicol, cefotaxime [4,16,26,30]. Most total coliform isolates in all parts of the river were highly resistant to most ß-lactam antibiotics and aminoglycosides [4,31]. There were no dominant resistance profiles, which indicated a wide heterogeneity of the isolated coliform bacteria

Table 1: Antibiotic resistance in ready-to-eat food products.

Microorganism	Food	Resistant/virulent Gene	Antimicrobial's resistance	Pub
Staphylococci *S. equorum, S. vitulinus*	pork ham, chicken, pork sausage, salami, pork luncheon meat	*mec*A gene, *Sei* enterotoxins, *seln* enterotoxin-like proteins, *eta* exfoliative toxin A	fusidic acid, cefoxitin	[18]
Bacillus *B. cereus, B. alvei,* *B. polymyxa, B. firmus*	milk products, RTE meat products, beverages, water	*nheA*, *nheB, nheC* haemolytic enterotoxins CAD, cytotoxin enterotoxin, enterotoxigenic genes	penicillin, amoxicillin, ampicillin cefixime, ceftazidine	[19]
Listeria *L.monocytogenes*	pre-chill carcasses, ground beef		ampicillin, vancomycin, gentamycin	[20]
	RTE artisanal food samples requiring minimal or moderate processing	hlyA, prfA, inlA	Ampicillin, sulfamethoxazole-trimethoprim	[21]
Acinetobacter Enterobacter *Klebsiella, S. Shigella,* *E.hormaechei*	*eko, fufu*, zobo food samples	MDR	Ampicillin, cephalothin	[22]
Klebsiella pneumoniae	ready to eat processed meat	*SHV*, *TEM*, *CTX-M15*, *AMPC*, *CIT-M*, *VIM*	β–lactam antibiotics, ceftazidime, cefotaxime, cefoxitin, ertapenem, amoxicillin-clavulanic acid	[23]
Salmonella *S. Typhimurium,* *S. Enteritidis, S. Typhi*	ready-to-eat food like rasmalai or chicken gravy	*inv*A, *Sdf* I, *Via B*, *Spy*	Oxacillin, Cefoxitin, Ampicillin	[24]
Enterobacteriaceae *Enterococcus faecalis, Macrococcus caseolyticus, Enterococcus faecium, Enterococcus caseliflavus, Staphylococcus haemolyticus, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus hirae*	Minas cheese	*mec*A, *smr*, *blaZ*, *msr*A, *msr*B, *lin*A, *aac*A-*aph*D		[25]
Citrobacter, Edwardsiella, *Enterobacter,E. coli,* *Klebsiella, Proteus,* *Salmonella, Serratia,* *Shigella*	ready-to-eat food	spvC invA	cefuroxime, nitrofurantoin, augmentin, ampicillin, gentamycin, ciprofloxacin	[26]
Salmonella Typhimurium *Salmonella Kentucky*	ready-to-eat food	MDR		[27]
Staphylococcus	Ready-to-Eat, mealworms	OXA−48, blaNDM−1	*Carbapenemase*	[28]
Staphylococcus, piscifermentans, *Citrobacter freundii*, *Enterococcus faecalis*, *Salmonella enterica*, *Staphylococcus aureus*, *Citrobacter werkmanii*, *Klebsiella pneumoniae*, *Macrococcus caseolyticus*, *Klebsiella aerogenes*, *Staphylococcus saprophyticus*, *Pseudocitrobacter anthropi*, *Citrobacter europaeus*, *Shigella sonnei*, *Escherichia fergusonii*, *Klebsiella grimontii*, *Burkholderia cepacia*, *Bacillus cereus*	*kargyong*, pork *kargyong*, *satchu*, *khyopeh*	MDR	gentamicin, cotrimoxazole, norfloxacin, trimethoprim	[29]
Enterobacteriaceae *E. coli (phylogenetic groups A, B1, D; none STEC)*	split or mixed leaves, carrot, corn	tet(A), tet(B), aadA, strA-strB, sul1, sul2, dfrA1, dfrA12, blaTEM	tetracycline, streptomycin, sulfamethoxazole, trimethoprim, ampicillin, nalidixic acid, ciprofloxacin, chloramphenicol	[30]
Enterococcus *E. casseliflavus,* *E. faecalis, E. faecium, E. hirae, E. gallinarum,* *E. spp*		tet(M), tet(L) erm(B	Tetracyclines, erythromycin, nitrofurantoin, ciprofloxacin [31,32]	

Where: CPS-coagulase-positive staphylococci; CNS-coagulase-negative staphylococci; TSST-1-toxic shock syndrome toxin 1; ET-exfoliative toxin; SE-staphylococcal enterotoxin; Sag-staphylococcal super antigen.

concerning the antibiotic resistance.

ARG in Contaminated Food Products

Metal-resistant bacteria is an additional aspect of bacterial survival and proliferation. In fact, both of them are associated since microbes and metal resistance correlates with antibiotic resistance and is encoded by both a chromosome and a plasmid. Hence, when associated with bacteria, it is encoded only by chromosomes.

Table 2 updates on the bacterial antibiotic resistance in specific food products. Based on laboratory experiments, the minimum inhibitory concentrations (MIC) for each heavy metal were identified. However, for natural populations of microbes, these concentrations often did not act as inhibitory. Therefore, the MIC were adjusted in accordance with the response of natural associations and then used to prepare selective media [16,35].

A high incidence of MDR microorganism in pediatric and adults' diarrheal patients was reported [66,67]. Interestingly, the link of those isolates to livestock clades suggests transmission to human via the food consumption. The existence of imipenem-resistant metallo-beta-lactamase (MBL)-production represent an emerging threat and causing concerns since they are one of the most common processes for feared resistance mechanisms [68]. It can be concluded that microbial antibiotic and metal resistances are related and their frequent co-habitation is driven by selective oxidative stress pressure. Exploring

Table 2: Bacterial antibiotic resistance in industrial processed food products.

Microorganism	**Food**	**Antimicrobial's resistance**	**Pub**
Listeria monocytogenes	Pre-chill carcasses, ground beef	ampicillin, vancomycin, gentamycin	[20]
	German Food Products	benzalkonium chloride, glutaraldhyde, isopropanol, glutaraldehyde; sodium hypochlorite, NaClo; peracetic acid, biocidal product containing bis(3-aminopropyl) dodecylamine.	[36]
Escherichia coli	Raw chicken	tetracycline, colistin, sulfonamide, chloramphenicol, cefotaxime	[37]
	Raw meat, fish, processed foods	Ampicillin, Chloramphenicol, florfenicol	[38]
		Sulfonamide, streptomycin,tetracycline, minocycline, doxycycline, oxytetracycline, chlortetracycline	
		tetracycline, minocycline, doxycycline, oxytetracycline, chlortetracycline	[39]
	Contaminated food derived from infected animals	cefotaxime	[40]
		cefotaxime	[41]
	Raw milk	resistant to 1-3 classes of antibiotics	[42]
O157:H7	Sheep and goat carcasses	Norfloxacin, polymixin-B, Ceftazidime, Kanamycin	[43]
ESBL-EC	Raw bovine, caprine milk	sulfonamide, colistin, gentamicin, tetracycline, quinolone, chloramphenicol	[44]
EPEC, EAEC, STEC	Processed foods	Cefuroxime, co-trimoxazole	[45]
E. coli, Klebsiella pneumoniae	Raw food material: mutton, poultry, fish, vegetables, fruits	Colistin	[46]
Campylobacter jejuni	Undercooked meat, raw milk, untreated water	Multiple antibiotic resistance: Metallo-β-lactamase ceftriaxone; ampicillin; chloramphenicol; tetracycline; streptomycin; ciprofloxacin; nalidixic acid; erythromycin; gentamycin; sulphomethoxazole/trimethoprim; tigecycline; imipenem	[47]
	Wild animals, birds	rifamycin, streptogramin, macrolide	[48]
	Raw milk, milk products	nalidixic acid, ciprofloxacin, tetracyclin	[49]
Pseudomonadaceae, Enterobacteriaceae, Yersiniaceae *E. coli, aerobic bacteria, coliform*	Raw milk	azide-resistant, ceftazidime, Tetracyclines	[50]
Staphylococcus aureus	Freshly processed pork, chicken carcasses	methicillin-resistant *S. aureus*	[51]
MRSA ST398	Bulk tank milk	Tetracycline	[52]
***Stenotrophomonas, Myroides, Pseudomonas* spp.**	Frozen meat, seafood	Trimethoprim + sulfamethoxazole, chloramphenicol	[53]
Gram-negative *Campylobacter, E. coli, Salmonella, Vibrio, Yersinia*	Raw meat, fish, plant products	aminoglycosides, cephalosporins, fluoroquinolones, penicillins, tetracyclines, sulfonamides	[54]
Gram-positive *Listeria, Staphylococcus*		fluoroquinolones, aminoglycosides, lincosamides, glycopeptides, nitrofurans, macrolides, tetracyclines, sulfonamides, penicillins, streptogramins	
Gram-positive *Enterococcus*		AM classes of Gram-positive	
Enterococcus	Raw materials, traditional cheeses	erythromycin, ciprofloxacin, quinupristin-dalfopristin, tetracycline, streptomycin	[55]
	Broiler chickens	Vancomycin, gentamicin	[56]
E. faecium, E. faecalis, E. *durans*, , E. *gallinarum*, E. *hirae*, *E. casseliflavus, E. mundtii*	Raw minced pork, fresh sausage	tetracycline, erythromycin, gentamycin ampicillin, oxacillin	[57]
Salmonella	Raw chevon, chicken	gentamicin, imipenem, ceftazidime, erythromycin, oxytetracycline	[58]
S. Typhimurium, S. Kentucky	Poultry carcasses	tetracycline, ampicillin, amoxicillin-clavulanic acid, ceftiofur, streptomycin, sulfisoxazole	[27]
S. enterica	contaminated food derived from infected animals	Streptomycin, chloramphenicol; tetracycline, ampicillin	[59]
Campylobacter spp.	Cross-contamination with other foods	Ciprofloxacin, erythromycin	[60]
Staphylococcus spp. *S. vitulinus, S. aureus*	Food stuffs	penicillin, cefoxitin, tetracycline	[61]
Clostridium difficile	Poultry litter	vancomycin, metronidazole, linezolid, tigecycline, moxifloxacin.	[62]
Achromobacter, Acinetobacter, Pseudomonas, Salmonella *E. coli, Pseudomonas spp., Acinetobacter spp., Bordetella trematum, Achromobacter spp., Ochrobactrum intermedium, Hafnia alvei, Raoultella ornithinolytica, Stenotrophomonas maltophilia*	Small-scale backyard poultry flocks	β-lactamase Carbapenem	[63]
Lactobacillus plantarum, L garvieae, L lactis, L. salivarius, subsp. lactis, L. reuteri, L. johnsonii, L. brevis, L. crispatus	Raw and processed pork, chicken products	Tetracycline	[64]
Actinobacteria Ferrimicrobium, Saccharomonospora Aeromicrobium	Fresh water	Rifamycin, aminoglycoside, macrolide, fluoroquinolone	[65]

resistance acquisition is important not only for an evolutionary perspective, but also to prevent and treat resistant bacterial food contamination and the ensuing infections.

Natural Antibacterial Activity

Although a bit out of the scope of the present review and in order to encourage non-antibiotic based new therapeutic strategies, natural antibacterial activities is described. While screening Google Scholar and PubMed databases, a plethora of natural antimicrobial components that serve to suppress antibacterial resistance of multiple types of microorganisms were identified (Table 3), [69]. Not surprising, multiple anti-virulence strategies are designed and are being developed as a new approach to fight pathogens [70-72].

Nowadays, enteric dysbiotic effects and complications are observed all over the world and are associated with multiple human chronic conditions [1,4,81, and 82]. Notably, food impacts the microbiome/dysbiome ratio and industrial processed food additives are potential drivers of many of those chronic diseases, including autoimmune and neurodegenerative conditions [33,83-87]. The close interrelationship between nutrients, dysbiotic/pathobiotic microbes and human chronic diseases [88] dictates some therapeutic strategies. Manipulating and redirecting food intake for a preventive, uncontaminated and healthier nutrition is one avenue. The second is to suppress the harmful bacteria by regulating antibiotic's usage thus diminish aggravate microbial resistance. The third strategy is to use a non-pharmacological approach to combat the pathobionts by natural antibacterial factors, thus suppressing ARG distribution.

The *Enterobacteriaceae* family is the most frequent infectious agents of bacterial originated acute gastroenteritis. For many years, functional milk fermented dairy products are used to prevent such diseases. They restore and normalize intestinal microbiota. A well-documented example is the enriched kefir drinks that suppress bacteria of *Enterobacteriaceae* family [4]. In fact, enriched kefir bio-products are capable to inhibit the development and proliferation of bacteria such as *Proteus mirabilis*, *Salmonella typhimurium, Shigella sonnei (S-form) and E. coli* 3912/41. Since kefir products are enriched with lactulose, this carbohydrate polymer encourage growth and enhance proliferation of *Lacto-* and *bifidobacteria*, hence antagonizing the enterobacteria.

A new non-antibiotic based and promising therapeutic strategy to fight ARG spreading is by identifying antimicrobial Peptides. It gives new hopes in the biomedical and pharmaceutical fields [89]. The immunoglobulin lactoglobulin is capable to suppress the pathogenic *enterobacteria*, by inhibiting their proliferation and growth, when compared to control samples [34]. Lactoferrin and its derived peptides represent an additional beneficial example [90]. Those new antibacterial compounds might help to fight the dysbiotic and pathobiotic microbes, including acute gastroenteritis caused by one of the *Enterobacteriaceae* family.

Several strategies can be used to suppress microbial virulence: surface adhesion inhibition, tissue invasion attenuation, toxin's suppression, and/or affecting gene regulation of other hostile features [68,69, and 78]. Disinfection with wash water is commonly applied to reduce bacterial populations on fresh-cut products, resulting in their increased shelf life. Chlorine (i.e., sodium hypochlorite solutions) and additional chlorine-based disinfectants act as oxidants to disturb cellular functions, including DNA replication, electron transport systems, membrane structure and metabolic enzymes of the microorganisms [91]. Indeed, chlorine-based sanitizers are most efficient when adequate doses are applied.

The usage of organic acids in the processed food industry affects the pH of the products [83]. In parallel, the food-borne pathogen *E. coli* O157:H7 is associated with the emergence of tolerance to the lower pH levels [75]. This phenomenon might be due to a rapid adaptation of the microbe to the changing nutritional processes and human habits, inducing tolerance to the organic acid's consumption. The presence of a large number of organic substances in the washing water and the soil contributes to a decrease in the functionality of organic chlorine-based disinfectants used. In fact, these large organic acids load also decreases the oxidation reduction potential. This results in the reduction of the disinfectant capacity of the chlorine in wash water. The food-borne pathogen *E. coli* O157:H7 has substantial adaptive mechanisms to overcome acidic pH and sublethal oxidative stress by developing self-defense factors that help the bug to survive in the gut lumen.

Several natural anti-infective compounds were detected from plants. Studying poaceous crops, such as rice (Oryza sativa) revealed several labdane-related diterpenoids like momilactones, phytocassanes and oryzalexins that help the crops to survive abiotic and biotic

Table 3: Natural antimicrobial factors.

Microorganism	Food	Natural antimicrobials	Pub
Listeria monocytogenes	Beef fat	long-chain unsaturated fatty acids	[68]
	Ready-to-eat, processed food	steam-distilled essential oil of *Cannabis sativa* L.	[73]
Lactobacillus plantarum *B21,* WCFS1	Ready-to-eat	plantacyclin B21AG, plasmid designated as pB21AG01, probiotic *L. plantarum* WCFS1	[74]
Escherichia coli *O157:H7*	Industrial operations to wash, sanitize fresh-cut	Chlorinated water.	[75]
	Maize (*Zea mays*)	β-Selinene, β-costic, a predominant derivative of ZmTps21 terpenoids.	[6]
K-12, O157:H7		sublethal pH: upregulated intergenic regions by H-ATR, L-ATR, A-ATR induction.	[76]
Campylobacter jejuni	*Chicken feces, human infections, contaminated foods*	allyl-isothiocyanate, benzyl isothiocyanate	[77]
Lactobacillus spp	Enzymatic complexes preventing the antibiotic-target interaction; Degradation of extra- or intra-cellular antibiotics by enzymes; Changing cell wall permeability or pump's activation to reduce antibiotic content intracellularly		[78]
B. amyloliquefaciens	Ethyl acetate extract against: *Staphylococcus aureus*, *Bacillus subtilis*, *S. epidermidis, Enterococcus cloacae.*		[79]
Echinochloa crusgalli L	EcAMP3 inhibits the growth of phytopathogenic bacteria		[80]
lactic acid bacteria	Secreted organic acids lower the pH, thus increase antibacterial activity of the LAB cultures		[69]

surrounding stresses [6,75]. In addition, complex organic compounds, namely, terpinoids were found in corn. They include sesquiterpenoids derived from β-macrocarpene and diterpenoids derived from entkaurans, called zelexins and kaura-lexins, respectively [6,75]. Regarding the maize diterpenoid defensive molecules, it appears that the specific ent-copalyl diphosphate synthase [6,75] is the only planta enzyme that is essential for kauralexin biosynthesis. Those acidic terpenoid phytoalexins mediate defense against pathogen attacking the maize above-ground branches [92]. Intriguingly, several antifungal compounds are corn originated, however the specific genes that contribute to this antifungal effect is largely unknown.

Thirty-two strains of lactic acid bacteria (LAB) were examined for the presence of probiotic and prebiotic potential activities against major MDR and pathogenic microbes in food [69]. Despite their potential benefit to prevent antibiotics resistance [93], one should remember their potential virulent factors, including the transfer of ARG via horizontal gene transfer (HGT) inside the gut lumen [33,94], thus risking the physiological microbiome equilibrium and eubiosis. In fact, HGT is the main mechanism of inheritance of mutational changes that impact bacterial evolution. By using three mechanisms: transformation, transduction and conjugation, harmful MGEs like ARGs can spread in between Prokaryotes and even land inside Eukaryotes. When the external genetic cargo, including the ARGs, carried by the ready to use and the contaminated nutrients come in contact with the microbiome, it represents a selective pressure that restructure the gut populations toward dysbiosis and even pathobiosis. In summary, over and abuse usage of antibiotics induces antibiotic resistance that find its way to the gut lumen, thus changing the enteric ecology and compromising the effectiveness of the antimicrobial drugs [33].

One of the most widely represented pathogenic species of microorganisms living in the environmental is *Listeria monocytogenes*. This microorganism is able to survive both in the presence of oxygen and in its absence [95]. *L. monocytogenes* is one of the most resistant microorganisms. According to literature, 30% of food-borne infections are fatal if they are caused by *L. monocytogenes*. For a while, the gold standard of antibiotics to eradicate *L. monocytogenes* were aminopenicillin or benzylpenicillin alone or in combination with aminoglycoside [95]. Even resistance to broad-spectrum cephalosporin antibiotics has been reported. Since *L. monocytogenes* is an intracellular microorganism, it inhibits anti-bacterial drugs from penetration into host cells and the subsequent elimination of the bacteria. The study of the effect of various plant components on the spread, reproduction and excretion of *L. monocytogenes* from cells led to the discovery and characterization of Cannabis sativa L essential oil against *L. monocytogenes* [73]. More studies are needed to study the properties those powerful suppressive bioactive phytochemicals like essential oils of various origins and the possibility to use them in the food industry aiming to fight the infectious diseases.

In addition to the previously described action of Cannabis sativa essential oil as one of the priority anti-bacterial agents, the properties of the following plant substances were studied: ethyl acetate and hexane extracts. They had significant antimicrobial activity against gram-positive microorganisms [76,80]. Ethyl acetate extract is active against *A. clavatus, A. fumigatus, A. niger* and *G. moniliformis* [96]. An interesting fact is that hexane and chloroform extracts have a more potent antifungal effect than ketoconazole.

Anti-infectious compounds from natural sources were reported as effective against *C. albicans, Cryptococcus neoformans, T. mentagrophytes and A. fumigates* [79].

The activity of those plant components is most probably due to their effects on the permeability of the cell membrane [96]. The isolated metabolomes of human *bifido* and *lacto* bacteria exposed anti-fungal activity. For example, *B. amyloliquefaciens* produces surfactin, iturine and phengicin [97]. Cyclic lipopeptides, such as Turin AE, bacillomycin D, F and L and *mycosubtilin*, were found to have an active antimycotic effect against different fungi. 3-phenyllactic acid has an antimycotic effect against *Aspergillus ochraceus, Penicillium roqueforti* and *P. Citrinu* [98]. It seems that the list of plant and bacterial natural anti-infectious factors is expanding. It is hoped that their isolation, categorization and usage might help combating the antibiotic resistance "pandemic."

E. coli evolutionary adapted protective mechanisms to survive the acidic environment of the enteric tract in both animals and humans is well known. In reality, acid resistance is one of the pathogenic factors of *E. coli* [76]. *Enterohemorrhagic E. coli* (EHEC) survives and contributes to the occurrence of outbreaks of sporadic food infections in products such as apple cider [99], meat sausages [100] and some other infected nutrients [76]. The food-borne contagious *E. coli* O157:H7 acquired multiple resistance factors, such as LysR, OxyR, lysA. Therefore, when using chlorine preparations, activation of OxyR is possible, which indirectly determines the resistance of this pathogen to oxidative stress [76]. To overcome the acid resistance of EHEC, the following two strategies can be applied: 1. acid neutralization [101]. 2. LAB secreted organic acids such as lactic, acetic and propionic acids reduce the pH level, thus, contributing anti-microbial activity. Their capacity to degrade lactose add additional susceptibility to commonly used antibiotics [69,96].

The often-used standard probiotic *L. plantarum* WCFS1 has the ability to conjugate plantacycline B21AG gene cluster [102]. This property confers the microbe the property to be used as a highly effective antimicrobial peptide against food infections. More so, unvirulent *Enterococcus* strains were reported to suppress *Clostridium botulinum* thus opening a new pathway to screen the genome of microorganisms by methods of directed mutation with subsequent evaluation of the gene structure [102]. All the above mentioned natural antibacterial compounds can substantially contribute to improved policy regulation, can strengthen and ameliorate infection control, epidemic surveillance and decrease the emergence and spreading of new resistant microorganisms. It will also serve as an opportunity to develop prebiotics and probiotic drugs as an alternative to antibacterial agents' consumption.

Conclusion

Environmental eco-events are important avenues, exposing human being to the surrounding antibiotic resistant microorganisms and some other harmful genes [33]. Livestock, wild animal and birds, plant reservoirs, sea creatures and contaminated industrial processed food products are integral participants in spreading bacterial resistance [103].

The monitoring of the sensitivity to antimicrobial drugs of these microorganisms allowed to calculate and predict the general trends of increasing antibiotic resistance of the studied pathogens. All the investigated strains had different antibioticograms to traditional drugs and significant variability in sensitivity to modern antibiotics with pronounced polyresistance in *Acinetobacter, Enterobacteriaceae, and Staphylococci* [4, 6, 97, and 102]. It is worth noting that only 4.8% of

chemical compounds were active against all the studied microorganisms [1,4, and 6]. The remaining compounds had less pronounced activity and acted only against single strains of microorganisms, or did not show antimicrobial activity at all against the tested strains.

The WHO has published several documents in the field of ensuring the safety of the use of antibacterial drugs in the agro-industrial complex, medicine, and pharmaceutical activities. These documents are fundamental for the field of preventing the emergence of resistant pathogens for all the countries all over the globus [4]. The WHO proposes to introduce a unified approach to combat the spreading of old and the emergence of new infections and in parallel, to attenuate the resistance to antibiotics and disinfectants used. At the heart of the "WHO Global Action Plan" approach, the main activities are detailed below.

The first component is an understanding of the possibility of professional communication in the areas of the use of antibacterial drugs. Then it is necessary to have a single database for all types of microorganisms determined by genetically determined resistance to antibacterial drugs [4,21, and 22]. Implementation of effective, unified measures in epidemiology, sanitation, contributing to the reduction of infections. The use of antibacterial drugs in animals and humans only according to approved protocols and standards, taking into account the possibility of the formation of resistant strains. The last component of this approach is economic investment in the study of new medicines, disinfectants, vaccines, and other activities. In addition to the Unified Approach, the WHO describes the obstacles to the surveillance of microbial resistance to antimicrobials. There is a competition between different areas of antibiotic users: agro-industrial complex, pharmaceutical industry, medicine. The approaches used in different countries differ significantly and do not allow an integral approach to solving the problem of resistance and surveillance of microorganisms to the antibacterial drugs used [21,22]. A schematic illustration of the environmental sources of the ARGs along the food chain and their impact on the human intestinal eco-events is present in figure 1.

General measures to address antimicrobial resistance in the wider environment include improved controls on pollution from industrial, residential and agricultural sources, street food and catering business [24,30]. In this regard, the new area of using probiotics to fight infection is expanding. Most recently, five LAB strains, selected from fermented products, were documented to suppress human intestinal lumen pathobionts [104]. Improved research as well as environmental monitoring and risk assessment is required to better understanding the role of the environment in various sections and spread of detrimental antimicrobial resistance.

The main purpose of the use of antibacterial drugs should be strictly for therapy according to approved indications. The use of antibiotics for prevention, growth promotion, in medicine and agro-industrial complex may become a new challenge to ensure public safety. A better control of the types and amounts of antimicrobials plus the numbers of resistant bacteria that are allowed to be placed into the environment, is highly recommended. A prime priority is to decrease the ARGs transferred via food intake, in order to minimize their entry into the intestinal, highly crowded microbials' inhabitants. What is vitally important is that more will be done to stop the distribution of multi resistant microorganism, not only from person to person but between and within the human and agriculture sectors, processed food facilities and the global environment.

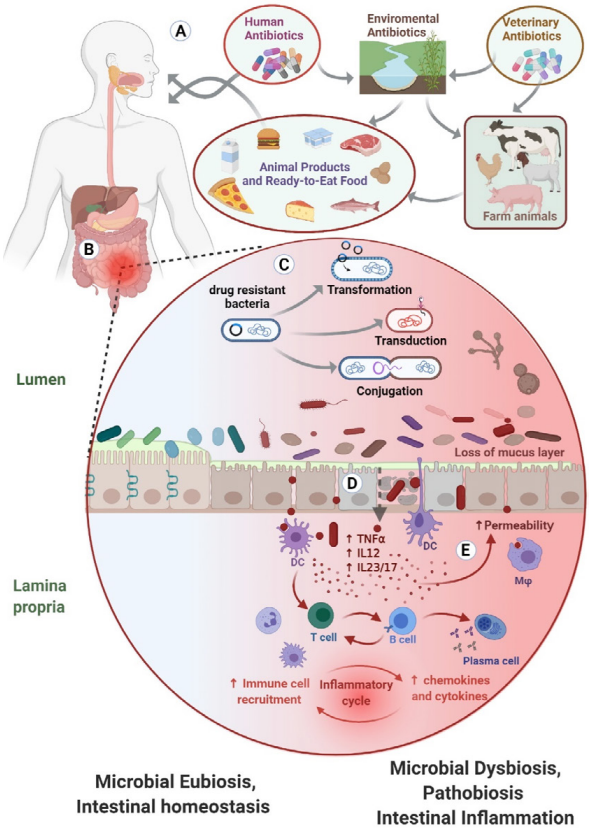

Figure 1: A schematic presentations of the environmental sources of the ARGs along the food chain and their impact on the human intestinal eco-events.

Figure Legend:

- Excessive consumption and inappropriate use of antimicrobial agents within and between various environments, such as farming, agricultural, industrial, hospitals and aquaculture, creates a strong anti-microbial evolutionary pressure. As a result, positive selection accelerates the emergence and thriving of microorganisms that possess multi-resistance genes, plasmid and other determinants.

- Transient bacteria with ARG and potential virulent factors reach the small intestine. Continuous antibiotic selective pressure that is imposed upon the gut microbiota, triggers a response almost immediately, via HGT mechanisms. This is well exemplified by the antibiotic excessive usage in this era, within the gut mobilome, resulting in the selection of certain genes and genotypes in the gut microbiome.

- The presence of ARG leads to disturbances in the ecological community of the gut microbiota. Presented here are three mechanisms of HGT. Transformation is a genetic modification as a result of acquiring foreign genetic material. This natural evolutionary capability is relatively common in bacteria and, to some extent, in archaea. Transduction allows microbial DNA to be transferred from one bacterium to another one by a viral intermediate. Conjugation is the transmission of DNA material during a cell-to-cell interaction. It is transferred from a donor to a recipient cell via an element such as transposon, plasmid, integrative and conjugative elements (ICEs) or other MGEs.

- Bacterial or viral infections disturb the fine tuning of the intestinal epithelium homeostasis by degrading the functional mucosal immunity and increased bacterial translocation. Moreover, this pathogenic activity damages the intestinal barrier mechanism by disrupting the integrity of inter epithelial tight junctions and by injuring the epithelial cell line, leading to an increase in intestinal permeability.

- These bacteria promote the activation of dendritic cells and macrophages by microbe-associated molecular patterns, thus increasing the release of proinflammatory cytokines and inducing neutrophil chemotaxis. Local inflammation leads to epithelial cells damage, and the recruitment of T-cells and B-cells response. The adaptive immune system reacts through a phase of activation and proliferation, thus, driving inflammation, which can ultimately lead to chronic diseases. Created with BioRender.com, Canada.

Abbreviations

ARG: Antibiotics Resistant Genes; MDR: Multidrug Resistance; MGEs: mobile genetic elements; MIC: Minimum Inhibitory Concentrations; LAB: Lactic Acid Bacteria; EHEC: Enterohemorrhagic E. coli; CFSs: Cell-Free Supernatants; ORP: Oxidation Reduction Potential; MBL: Metallo-Beta-Lactamase; HGT: Horizontal Gene Transfer; ICE: Integrative and Conjugative Element.

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The three authors agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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