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Culprits of Antibiotic Resistance

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Abstract

Antibiotics are secondary metabolites produced by micro-organisms which act against other organisms. The producing organisms are protected from its harm by various methods. These are life-saving miracle drugs which are used not only for human diseases but also as growth promoters in animal husbandry, agriculture, food processing etc. This has made bacteria resistant to these miracle drugs which has hampered human health especially the high-risk patients like immune-compromised, organ transplants, HIV or even Corona infected patients causing increase in fatality rates. To put in the words of Johusa Lederberg "Antibiotic resistance as a phenomenon is, in itself, not surprising. Nor is it new. It is, however, newly worrying, because it is accumulating and accelerating, while the world's tools for combating it decrease in power". Therefore, now the time has come to decide between more trade and human life. The review discusses these aspects along with different ways which has increased drug resistance.

Keywords: Antibiotics; Secondary metabolites; Miracle drugs; Antibiotic resistance; Human health

Introduction

Food is the basic need of life. All living beings require food to carry out the basic metabolic activities, energy and growth. Increasing world population (7 billion at present estimated to be 9 billion by 2050) demands increased food. Human beings since ancient days have been consuming food from plants, animals as well as ocean. Earlier humans killed land animals or sea animals for survival; later, primitive humans consumed roots, barks, leaves, flowers and fruits available in jungles. Observing that seeds thrown by them gave rise to new plants has led to farming or agriculture as well as animal husbandry and aquaculture farming. Today consumers require healthy and safe food. The human body parts like skin, genitals, airways, urinary tract and gut are a house of numerous bacteria, fungi and viruses. These have a complex relationship amongst each other and the human host. Antimicrobial Resistance (AMR) persists and such organisms proliferate naturally in the environment (Figure 1). This is a global health crisis. Currently, AMR contributes to approximately 700,000 deaths annually and it is estimated to rise to 10 million deaths per year in 2050 [59]. Furthermore, by 2050 AMR could cost $100 trillion in lost economic output [60]. Therefore, understanding environmental hotspots such as agriculture, food processing, aquaculture systems for genetic exchange of AMR genes and determining their route of transfer to clinically relevant strains is very important [75].

Antibiotic Resistance from Agriculture

Agriculture requires soil, water and fertilizers. Soil is a natural environment for many antibiotics producing organisms which have developed resistance to the antibiotics they produce. The water used could be contaminated by various methods, the human waste streams, veterinary wastes or even dust [36]. The seepage of medical or pharma waste through ground water directly to the soil is possible. This is true for water soluble antibiotics like amoxicillin, tetracyclines, sulphamethazoles, neomycin etc. which are commonly prescribed to humans too. The raw animal manure used for fertilization of soil, irrigation with waste water can also cause deposition of antibiotics in the farm environment. The reason for this is all the antibiotics degrade at different rates [51]. The soil organisms under pressure may develop antibiotic resistant genes to out compete their counterparts. The resistant bacteria have been characterized from different vegetables like cabbage, radish, corn, onion which were grown on soil fertilized with animal manure and irrigated with waste water. However, vegetables may be contaminated by numerable pre- and post-harvest operations like manure, soil, irrigation water, equipment used for processing, harvesting and transportation and therefore, if consumed raw can cause entry of resistant bacteria in humans [7].

Biocides like triclosan, quaternary ammonium compounds,

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glutaraldehyde, iodophors have applications in numerous fields like health care settings, slaughter houses, veterinary practices, food industries, transportation for killing bacteria and in today's Corona crisis to decontaminate containment zones. These are also used in animal husbandry, farm buildings, barns, equipments, vehicles for decontamination.

Personal Care Products also Contribute to AMR

Cosmetics, personal health care products, house hold products and textile also use biocides. Consumers today are aware about microbial contamination, infection, removal of foul odor and need of pathogen free products. Moreover, mass media gives publicity to hospital cleanliness and removal of super bugs including Corona virus nowadays by usage of certain biocides and sanitizers thereby providing marketing and distribution of these biocides to the better-informed consumers. This is a main cause of rise in antibiotic resistance in health, veterinary and food sectors. These biocides especially triclosan and quaternary ammonium compounds have been shown to develop resistance in *Salmonella Typhimurium* by alteration of metabolic pathways [76]. *Mycobacterium* is shown to have natural resistance to 2% glutarldehyde [20]. The main cause of resistance is activation of efflux pumps in many bacteria like *Escherichia coli*, *S. Typhimurum*, *Staphylococcus aureus*, *Campylobacter jejuni*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Acinetobacter* [50]. The sublethal concentration of biocides causes stress in bacteria and expresses genes for stress regulation like *sox*R, *mar*A which are also regulators for antibiotic resistance which probably is responsible for cross resistance to antibiotics [18,46].

Food Processing and AMR

Industries discovered innovative ideas to meet increasing consumer demands. Increasing the production of agricultural commodities as well as development of better varieties of crops and food preservation became a priority. Food processing is an essential part of food industry to meet the consumer demands of ready to cook/eat food which are healthy, properly packed and microbiologically safe and shelf stable. These processing techniques include age old preservation techniques like drying, salting, pickling, acidification or modern methods like pasteurization, cooling, freezing, modified atmosphere packaging, uv treatment, irradiation or combination [1] which help in control of bacterial growth but may also cause stress in bacterial cells. The different stresses like acid stress, heat or cold stress or addition of preservatives may trigger bacterial mechanisms to adapt to these and also induce antibiotic stress [65,77]. Bacteria also possess several systems that can counteract stress which may be used during food processing thus developing resistance [74].

Animal Husbandry and Veterinary

In animal production antibiotics have been used as growth promoters to increase weight, feed conversion and reducing stress related diseases while transport of these animals. Moreover, in veterinary practices antibiotics are used to treat enteric disease in cows and pigs as well as mastitis in dairy cattles. The major classes of antibiotics aminoglycosides, beta-lactams, fluoroquinolones, macrolides, sulphonamides and tetracycline used for human treatments widely are a part of veterinary medicines too. Bacteria are known to adapt to the environment with antimicrobials. During food processing a zoonotic antibiotic pathogen may contaminate during slaughter and consumption of this food by humans may cause infection which will be difficult to treat or a resistant non-pathogen may transfer a genetic determinant to one of the potential pathogen or commensals in human gut or consumption of raw food can directly transfer the resistant pathogen to human beings [53]. Use of gentamicin and apramycin in animal feed has been showed to have followed emergence of *E. coli* and *Salmonella* species resistant to these drugs; ceftriaxone resistant isolate of S. typhimurium has also been isolated from a pediatric patient and traced in some cattles. An antibiotic resistance profile of *Salmonella* spp. isolated from healthy animals matched the antibiotics used in the animal feed [14,64]. Several authors have shown phenotypic increase in antibiotic resistance in *E. coli*, *S. Typhimurium* and *S. aureus* the common food-borne pathogens due to acid stress, heat stress or altered pH [30,54]. *Cronobacter sakazakii* an emerging food-borne pathogen often found in infant formula was tested for antibiotic resistance against 13 antibiotics after exposure to combination of any of sub-lethal treatments of cold stress, heat stress, acid stress and alkaline stress became resistant to at least 4 out of 13 antibiotics and combination with heat stress developed more resistance than cold stress [2]. This is probably because the cells may become competent and cause horizontal gene transfer. A link between increased antibacterial resistance in *E. coli* and SOS response after exposure to stresses like uv treatment and high pressure have also been reported [16].

Fishing and Aquaculture are also Culprits

The global fish production of 179 million tons [27] including aquaculture is one of the most important sources of animal protein and is the fastest growing sector. To meet the demands of growing human population and approximately 80% reduction in fishing stock aquaculture has become sustainable and reliable source of food [26,61]. Approximately 580 varieties of fish including 362 finfish and 63 crustaceans are cultivated under wide range of growth parameters for maximum cultivation [26,57]. In the European countries the antibiotics used in aquaculture is under the control EU Veterinary Medicinal Products Directive, while USFDA controls in USA [22-24]. However, most of the world aquaculture (90%) is practiced in developing countries which do not have strict regulations [15]. Use of antibiotics as growth promoters is common in shrimp [38] and salmon [12] farming and in case of finfish as individual fish cannot be treated entire population is treated with antibiotics [11,21]. Antibiotics used as human medicines like oxytetracycline, florfenicol, and amoxicillin are often used in aquaculture farming [59]. This industry heavily depends on antibiotics for general site distinction and treatment of fish and shellfish diseases. Farmed trout, tilapia and salmon from 11 countries including the US, China, Mexico, Thailand, Scotland, and Canada showed presence of significant levels of tetracycline, macrolide and sulfonamide [19]. The antibiotic residues being non-biodegradable are consumed by humans on consumption of such fish or shell fish [11,68]. Aquaculture farms are rightly called genetic reactors or hot spots for transfer of AMR genes [5,55]. Besides this many heavy metals like Cu and Cu alloys are used as anti-fouling agents and for making cages and nets. Fish feed also contain cadmium, iron or lead which may reach water sediments and help in co-selection of antibiotic resistance in marine environment. Strains isolated from fish and eel aquaculture was found to be resistant to antibiotics and heavy metals. The strains also harbored plasmids, integrons and gene cassettes for antibiotic resistance [42,62]. Integrated fish farming is practiced in Asia and Africa wherein fish or shellfish are reared in ponds where cattles and livestocks like pigs, and poultry are located over or near a pond, allowing drainage of livestock manure and excess feed into the pond as direct feed for fish and/or as fertilizer for phytoplankton and other live fish feed [48]. This farm grown animal is extensively reared on antimicrobials as growth promoters and for prophylaxis [37]. The antibiotics are same as those used for human medicines. Thus, aquatic bacteria come in contact with terrestrial bacteria and transfer of antibiotic resistance genes can occur. Other co-pollutants include storm-water runoff, agricultural waste contamination and discharges from sewage water potentially co-select transfer of resistance. Integrated chicken-fish farms in Thailand showed significant increase in resistance of *Acinetobacter* spp. to six different antibiotics within two months of new fish production cycle [63]. Although considerable studies have been performed in food production areas such as pig and poultry farming, there is currently a lack of extensive studies in aquaculture systems. Whatever, the pathway of transfer the transfer of AMR genes is detrimental for piscine as well as human health (Figure 2).

Lifestyle Another Culprit

The changing life styles have been gifted with diseases like obesity and diabetes mellitus or type 2 diabetes. Nonnutritive sweeteners like saccharin, sucralose, aspartame and acesulfame potassium have been approved U.S. Food and Drug Administration [31] as sugar substitutes in various foods and beverages. The global consumption of these sweeteners has increased to 117,00 metric tons annually because they are sweet and of lower calorie values [35]. After consumption they pass through human gastrointestinal tract and directly to waste water plants. Recently, it has been observed that these nonnutritive sweeteners can cause DNA damage in bacteria [4,66] which in turn can activate SOS response. Antibiotic Resistant Genes (ARG) transfer are known to be related to SOS response [6,78] have shown for the first time that these nonnutritive sweeteners can promote ARG transfers at environmental and clinically significant levels to *E. coli* MG 1655 and *Pseudomonas alloputida* by increase in cell membrane permeability and ROS production. The variety and enormous bacteria present in environment and human gut can further enhance ARG transfers. Modernization has also increased demands of minimally processed, Ready to Eat and Ready to Cook products. The RTC chilled and frozen poultry and fish samples were found to be contaminated with multidrug resistant *Salmonella* from India [32,43] similarly, emerging pathogens *Cronobacter sakazakii* and *K. pneumoniae* resistant to beta-lactams were detected in milk powder, sprout and fish samples [32].

GRAS Chemicals

Some GRAS chemicals are added as flavor enhancers, emulsifiers stabilizers, coloring agents, textural agents, sweeteners may be added to food to maintain its quality and safety till expiry date. These chemicals like salts, sorbates, benzoates, vinegars or acidulants or natural spices and flavoring agents with antimicrobial properties [28]. These chemicals like salts, sorbates, benzoates, vinegars or acidulants or natural spices and flavoring agents are known for antimicrobial properties since ancient days and are used since olden days [40]. However, food-borne pathogens like Enterohemorrhagic *E. Coli* (EHEC), *S. Typhimurium*, *L. monocytogenes* are known to tolerate acid stress [29]. Similarly, innate resistance to sorbates have been observed in *Sporolactobacillus*, certain molds like *Aspergillus*, *Fusarium, Geotrichum Mucor, Penicillium* and yeasts like *Candida*, *Saccharomyces* and *Torulopsis* [17]. Bacteria including *Bacillus*, *Corynebacterium*, *Micrococcus* and molds like *Aspergillus* are resistant to benzoates as they can degrade benzoate to succinate and acetyl CoA by β ketoadipic pathway [17].

Friendly Bacteria are also Demons

Russian scientist Elie Metchnikoff a century ago first proposed the use of "friendly bacteria" to delay aging and enhance health [49]. These are the probiotics which have shown to be extremely beneficial organisms especially to the human gut flora [44,56]. Researchers have observed probiotics can regulate gut flora, improve bioavailability of nutrients as well as immune system [41,70,73]. Other benefits include reduction in symptoms of lactose intolerance, treating or preventing gastrointestinal infections, reduction in mammary cancer, pulmonary damage due to viral infections, cholesterol and cardiovascular diseases [25,67,69,79]. These excessive benefits of probiotics have made them popular as food supplements in dairy products like yogurt, cheese and milk. They are also common in animal feed which leads them directly to human gut through food chain [71]. Probiotics are mixture *Lactobacillus* spp. which have GRAS status and therefore are not harmful**.** However, they are known to possess antibiotic resistant genes like *van*X, *van*E, *gyr*A, and *tet*M genes coding for resistance to vancomycin, ciprofloxacin and tetracycline antibiotics respectively [34,45] have shown that *Lactobacillus* also possess *erm*B and/or *tet*W, *tet*M genes that contribute resistance to clindamycin, and/or erythromycin and oxytetracycline respectively. The presence of *aac (60)-aph (20)-Ia* coding for gentamicin resistance and *aad*A gene coding for resistance to streptomycin and spectinomycin have also been observed in *Lactobacillus* [9]. The potential transfer of these genes to human gut flora and eventually to opportunistic pathogens which reside in the human gut can cause severe clinical problems [8,33,39]. This fear of transfer of vancomycin resistant genes from one *Lactobacillus* species to another or to a pathogen like *Staphylococcus* or from *Enterococci* to *Lactobacillus acidophilus* has been demonstrated invitro as well as in the mice gut [52,72]. Therefore, although probiotics restore the gut flora, re-establish colonization resistance and eliminate pathogens; building up of antibiotic resistance genes in the gut causing a long-term problem outweighs the benefits. Development of next -generation probiotics must take into account these problems. Other probiotics like *Bifidobacteria, Enterococcus,* and *Streptococcus* must also be studied using new methods of antibiotic determinants like mathematical models, next generation sequencing studies, proteomics etc. [80]. The alternatives like use of phages, bactericidal peptides, non-antibiotic drugs and quorum quenching may also be adapted instead of antibiotics other non-antibiotic approaches to prevent or eliminate pathogens [3,13,47,58].

Conclusion

Antibiotic resistance is an ancient problem in new coat. Developing new antibiotics is not the solution. Creating awareness amongst every layman to minimize its use essential. Finding answer with the help of antibiotic stewardship programs around the world is required or another pandemic creating more disasters than the ongoing Corona war may follow. This warning was given the discoverer of the first magic bullet Sir Alexander Fleming himself.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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