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REVIEW ARTICLE

Possible Alternative Strategies to Combat Antimicrobial Resistance

Elsayed A. Abd El-Aziz, Sawsan M.A. El Sheikh, Azza Galal, and Yomna Refky*
Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, Zagazig, 44511, Egypt
*Corresponding author e-mail: yomnarefky@gmail.com

Abstract

Antibiotics are regarded as one of the twentieth century's most important discoveries, but antibiotic-resistant microorganisms rapidly appear when humans and animals use antibiotics carelessly. Unfortunately, antibiotic resistance has taken on international significance in recent years as the primary cause of death and economic catastrophe worldwide. Finding and creating innovative techniques to tackle antibiotic resistance is urgently required. The antibiotic resistance challenge cannot be solved by new medications alone. This article highlights the causes, mechanisms of antimicrobial resistance (AMR), and the adverse effects brought on by its widespread occurrence. Additionally, it focuses on the other novel approaches that may show effectiveness in controlling and combating AMR, including, certain physicochemical methods, antimicrobial peptides, medicinal plant, bacteriophage, probiotics, synobiotics, prebiotics, fecal transplants, and nanoparticles. These alternative approaches may become promising methods to enhance both human and animal health and decrease the unnecessary use of antibiotics. Governments, institutions, and regulatory agencies should work together to develop innovative strategies for enhancing antibiotic efficacy through novel targets.

Keywords: Antimicrobial resistance, Resistance management, Antibiotic alternatives, Nanotechnology and Medicinal plants.

Introduction

The innovation of penicillin by Sir Alexander Fleming is a significant turning point in human history. This achievement had prevented the spread of bacterial illnesses among Second World War soldiers, and rescued millions of lives [1]. Antibiotics are chemical substances produced by living microorganisms and aid the immune system in demolishing them [2]. Antibiotics can be produced by microbial fermentation or by exploiting the existing antibiotic backbone structure in a semi-synthetic process [3]. In the final phase microorganisms of the microbial stationary growth phase, bacteria produce antibiotics as secondary metabolites at a subtherapeutic dose [4]. Some antibiotics act via: i) inhibiting bacterial cell wall formation as glycopeptides, bacitracin and beta-lactams; ii) interfering with protein synthesis as aminoglycosides, tetracyclines, macrolides, lincosamides; iii) inhibiting (DNA) gyrase as quinolones; iv) inhibiting RNA synthesis as ansamycins, and v) suppressing the folate synthesis as sulphonamides [5].

The unlimited spread of resistance to antibiotics among bacteria causes thousands of deaths every year. It is a catastrophe that more microorganisms are becoming resistant to widely used antibiotics, particularly medications of last choice such as polymyxin, tigecycline, vancomycin, daptomycin [6]. The World Health Organization (WHO) viewed the antimicrobial resistance

(AMR) issue as a serious global health threat [7]. The most common way that antibiotic-resistant strains in particular zoonotic bacteria are transmitted from animals to humans is through the ingestion of tainted animal products (eggs, milk, or meat). About half or more of the isolated *Staphylococcus aureus* strains in Morocco tested positive for resistance to beta-lactam antibiotics, more than 28% to tetracycline, 24% to erythromycin, and less than 20% to ciprofloxacin after examination of samples taken during slaughter broiler chickens [8]. Another Zoonotic bacteria such as *Salmonella, Escherichia coli (E.coli),* and *Listeria monocytogenes,* are top priority for antimicrobial resistance [9], as *Salmonella* cause enteric fever, and gastroenteritis [9], *L. monocytogenes* infection may lead to septicemia, encephalitis, meningitis, abortion, still-births, and/or neonatal infections [10], *E. coli* is the most common pathogen leading to uncomplicated cystitis, and also results in other extraintestinal illnesses, including pneumonia, bacteremia, and abdominal infections such as spontaneous bacterial peritonitis [11].

In the 1970s, an outbreak of hospital-acquired (nosocomial) infections was brought on by the methicillin resistant *S. aureus* (MRSA) strain. Because the infection results in the creation of a mutated penicillin-binding protein (PBP2a), which inhibit the antibiotics from connecting with their intended binding site of action, treating MRSA infections with drugs having a-lactam ring is unsuccessful. This kind of resistance is regulated by the *mecA* or *mecC* gene [12].

1. Antimicrobial Resistance: A Worldwide Public Health Emergency

Antimicrobials are the most important forms of chemotherapy despite the different types of drugs discovered in medicine. They saved many lives and contributed to the avoidance and treatment of numerous bacterial diseases, which for several years were the main reason of morbidity and mortality in humans. Discovering many antibiotics between the 1950s and 1970s, the golden era of antibiotic discovery, no new classes discovered since then [13].

It is expected that by 2050, AMR will cause millions of deaths worldwide due to decrease the effectiveness of antibiotics used nowadays and the absence of novel antibiotics in development [14].

2. Types of antimicrobial resistance

The types of antimicrobial resistance include multi-drug resistance (MDR); extensive drug resistance (XDR) and pan-drug resistance (PDR). Multi-drug resistance is a bacterium that isresistant to at least one antibiotic from at least three groups. Extensive drug resistance means bacteria do not respond to at least one antibiotic in all but two or fewer antimicrobial classes. While pan-drug resistance refers resistance to all antibiotics from all antimicrobial groups and it is the most dangerous one [15]. Because of the considerable phenotypic and genotypic variety, as well as adaptation to environmental conditions, many microorganisms become resistant to most of antimicrobials used nowadays [16].

3. Causes of antibiotic resistance

There are many causes lead to the evolution and occurrence of AMR including:

3.1. Overuse of antibiotics without restrictions

The excessive misuse of antibiotics is one of the main causes of arising the AMR [17]. Antibiotics are usually used without restrictions and are available for people who do not have a prescription. This shortage of regulations results in antibiotics have become easily obtainable, cheap, and plentiful, which promotes misuse. Also, the online purchasing of these medication makes the AMR problem get worse [18].

3.2. Inappropriate Prescribing

According to several research, every 30% to 50% of cases reliable to AMR due to inappropriate treatment indication, misdiagnosis of the causative agent, or duration period of the antibiotic treatment is not enough [19]. Additionally, it has been discovered that between 30% and 60% of the antibiotics described in critical care units (ICUs) are inappropriate, ineffective, or unneeded [19]. Sub-inhibitory and sub-therapeutic antibiotic doses can accelerate the mutagenesis and genetic abnormalities of the microorganism [20].

3.3 Unnecessary using of antibiotics in veterinary medicine

Antibiotics given to food-producing animals for a many reasons, such as therapeutic, prophylaxis (protecting the animal from pathogen by giving it some antimicrobial) metaphylaxis (giving antimicrobials to animals when it get contact with diseased animal), and as a growth promotors which are given to animals in low dosages (sub-therapeutic) in feed or water to improve the growth and the production efficiency [21]. Between 2017 and 2030, scientists predicted that the consumption of antibiotics by food producing animals will reach 11.5% [22]. The overuse of some antibiotics such as penicillin, tetracycline, sulfonamides, chloramphenicol, fluoroquinolones increase the resistance incidence of *E. coli* strains [23]. Recurrent exposure to sub-therapeutic doses of antibiotics alters the intestine beneficial bacteria and encourages the rise of pathogenic microbes and genes that are resistant to both the antibiotic being used and other antibiotics [24].

Most of antibiotics sold in the U.S.A. are used in animals, mainly used for prophylaxis or as a growth promotor [25]. Farm animals initially transferred resistant bacteria to people over thirty years ago, because of the presence of high rates of antibiotic resistance were discovered in the gut microflora of both farm animals and farmers [26]. Antibacterial products used for hygiene or cleaning may potentially contribute to this issue, as they may interfere with the development of immunity against environmental antigens in adults as well as kids [18].

3.4. Impacts of environment

The major reservoir for many pathogens transmission is the environment [27]. Many factors as improper sanitation, pollution, organic fertilizers, and industrial waste products serve as reservoirs of infections and contribute to the environmental resistome [28]. In the developing world, most pesticides containing antimicrobials exceed the safety limits in edible crops. For example, over 90% of eggplant and about all of tomato and chilli goods exported to Nepal from India contained antimicrobial pesticides residuals [29]. Antimicrobial contamination of soil and water ecosystems may allow MDR bacteria to emerge through metabolic pathways [30]. Antimicrobial resistance has been observed in numerous

Salmonella strains among commercial swine farms after manure treatments [27].

3.5. Availability of Few New Antibiotics

A worrying scenario has arisen because of the increasing gap between the necessary need for new antibiotics in public health and the decreased likelihood of new antibacterial drug development. Major pharmaceutical companies have given up on developing new antimicrobial medications despite the continuous need for them, because of the high expense of clinical trials, other novel regulatory uncertainties over approval standards, as well as a low rate of return on investment [31].

4. Mechanism of Antibiotics Resistance:

There are many mechanisms used by bacteria as self-defense against antibiotics (Table1).

Table (1): Mechanisms of resistance to each class of antibiotics

Mechanism	Antibiotic	Reference
Efflux pumps	Fluoroquinolones, β-lactams, tetracycline and linezolid	[32]
Modification of target molecule by alteration in the ribosomal subunits	Macrolides, chloramphenicol, tetracycline, and aminoglycosides	[33]
Modification of target molecule by alteration in the PBPs	β-lactams	[34]
Modification of target molecule by alteration of the cell wall precursors	Glycopeptides like vancomycin	[34, 35]
Mutation in both topoisomerase IV and DNA gyrase	Fluoroquinolones	[36]
Antibiotic inactivation by Beta-lactamases	β-lactams	[37]
Antibiotic inactivation by AME's	Aminoglycosides	[38]
Antibiotic inactivation acetyltransferases	Chloramphenicol	[39]

AME's: Aminoglycoside modifying enzymes, PBPs: penicillin or membrane binding proteins, β-lactams: Beta-lactam antibiotics

4.1. Efflux pumps

Before the antibiotics bind to their intended target, the efflux mechanisms pump drugs out of the bacterial cell [40]. The cytoplasmic membrane contains these pumbs as opposed to porins, which are situated in the outer membrane. Efflux systems can be activated by antibiotics of all classes except for polymyxin [33].

4.2. Modification of target molecule

Modifications in the antimicrobials' target sites, which prevent medications from interacting with them, are another often occurring route of resistance. Target site alterations are commonly caused by mutation in bacterial gene's spontaneous chromosomal [5].

4.2.1. Alteration in the ribosomal subunits

Some important classes of antibiotics are macrolides, chloramphenicol and tetracycline, aminoglycosides that inhibit amino acid formation and protein synthesis by acting on 50s and 30s ribosomal subunits, respectively. Resistance occurs by modification occurs

to their binding sites on the ribosomes [33].

4.2.2 Alteration in the penicillin or membrane binding proteins (PBPs)

Mutations in the PBPs decrease the protein's affinity for β-lactam antibiotics. This process explains why *Streptococcus pneumoniae* and *Enterococcus faecalis* are resistant to penicillin and ampicillin, respectively. Similarly, *S. aureus* exhibits methicillin and oxacillin resistance [34].

4.2.3. Altered cell wall precursors

Glycopeptides like vancomycin or teicoplanin, which bind to residues of peptidoglycan layer called D-alanyl-D-alanine, can prevent Gram-positive bacteria from synthesizing cell walls by inhibiting this process. A resistance to glycopeptides develops because of formation of D-alanyl-lactate from D-alanyl-D-alanine [34].

4.2.4. Mutation in both topoisomerase IV and DNA gyrase

The quinolone group act via inhibiting the activity of DNA gyrase which encoded by (genes *gyr* A and *gyr* B) and topoisomerase IV which encoded by (genes par C and par E). Mutations in genes *gyr* A of DNA gyrase and *par* C of topoisomerase IV cause failure of the replication resulting in preventing fluoroquinolone (FQ) from binding [36].

4.3. Antibiotic inactivation

Some classes of antibiotics are inhibited by three enzymes such as β-lactamases, chloramphenicol acetyltransferases (AACs), and aminoglycoside-modifying enzymes [41].

4.3.1. Beta-lactamases

Nearly all beta-lactams with amide and ester bonds, such as carbapenems, monobactams, cephalosporins, and penicillin are hydrolyzed by lactamases. There are now over 300 identified – lactamases [42].

4.3.2. Aminoglycoside modifying enzymes (AMEs)

Adenylyl-transferases, nucleotidyl-transferases, or phosphoryl-transferases are the enzymes that deactivate aminoglycosides. Aminoglycoside-modifying enzymes (AMEs) have been found in the strains of *S. aureus*, *S. pneumoniae*, and *E. faecalis*. AMEs decrease the affinity of a modified molecule and inhibit aminoglycosides from binding to the 30S ribosomal subunit [43].

4.3.3. Chloramphenicol-acetyltransferases

Chloramphenicol transacetylase is an enzyme, which inhibit chloramphenicol compound by acetylation of the hydroxyl groups in its molecule, is present in some strains of *Hemophilus influenzae* and some Gram-positive and Gram-negative bacteria that are resistant to chloramphenicol. A ribosomal 50S subunit cannot be adequately bind to by modified chloramphenicol [39].

5. *Consequences related to the spread of antibiotic resistance*

a) Long period of illness due to complications of diseases and a high incidence of death.

b) Extended stays in hospital and diseases.

c) Increase the possibility of the spread of diseases between people.

d) Antibiotic treatment should be shifted to second generation or third-line antibiotics when a first-line antibiotic is no longer effective, and failures

of antibiotic prophylaxis lead to increase the incidence of bacteremia [44].

6. Antimicrobial resistance and food safety

Food safety is an important component of the food supply chain since it affects the final product's quality and, in turn, consumer acceptance [45]. Recently, a lot of enterprises have adopted the food supply control program. These programs consider any process-related risks that can jeopardize the safety of the finished product. Accidental or unplanned chemical or microbiological contamination of the product during the production process is one of the most frequent dangers [46].

Food has a vital role in the spread of harmful pathogens and AMR spoilage. Increase in AMR bacteria in food would be detrimental to human health [47]. Direct exposure to AMR bacteria occurs when an individual comes into contact directly with biological components or infected animals (such as saliva, blood, feces, urine, or semen) while indirect exposure occurs when an individual consumes food [48]. The main source of existence of resistance in the food chain is foods originating from animals [49]. Infected beef, pork, eggs, poultry, and turkey meat are typically liable for the spread of AMR Salmonella [50]. Some residues of antibiotics act like allergens which stimulate allergic reactions causing serious symptoms manifest as acute interstitial nephritis, erythema multiforme, skin rashes, hemolytic anemia, serum sickness, thrombocytopenia, vasculitis, toxic epidermal necrolysis, and Stevens–Johnson syndrome [51]. People who consumed tainted meat [52] have been diagnosed with allergic responses linked to antibiotic residues. The existence of residues of antibiotics in food had a potential role in liver affection with hepatotoxicity [53], carcinogenesis, teratogenicity, mutagenesis, and reproductive disorders [54]. Consumption of contaminated food with antibiotic residues affects the intestine microenvironment causing dysbiosis which leads to problems such as damaging the intestinal, obesity, and increased food allergy [55].

7. Route of resistance transmission to human

Zoonotic illnesses constitute about 60% of all human pathogens and 75% of developing diseases that harm people [56]. The primary means of spreading resistant microorganism and resistance genes from food animals to humans are food products of animal origin that are tainted with resistant bacteria. Direct interaction with animals or an environment where animals are present. Foods like fruits and vegetables that have been tainted with animal feces or contaminated water are also a problem [57, 58].

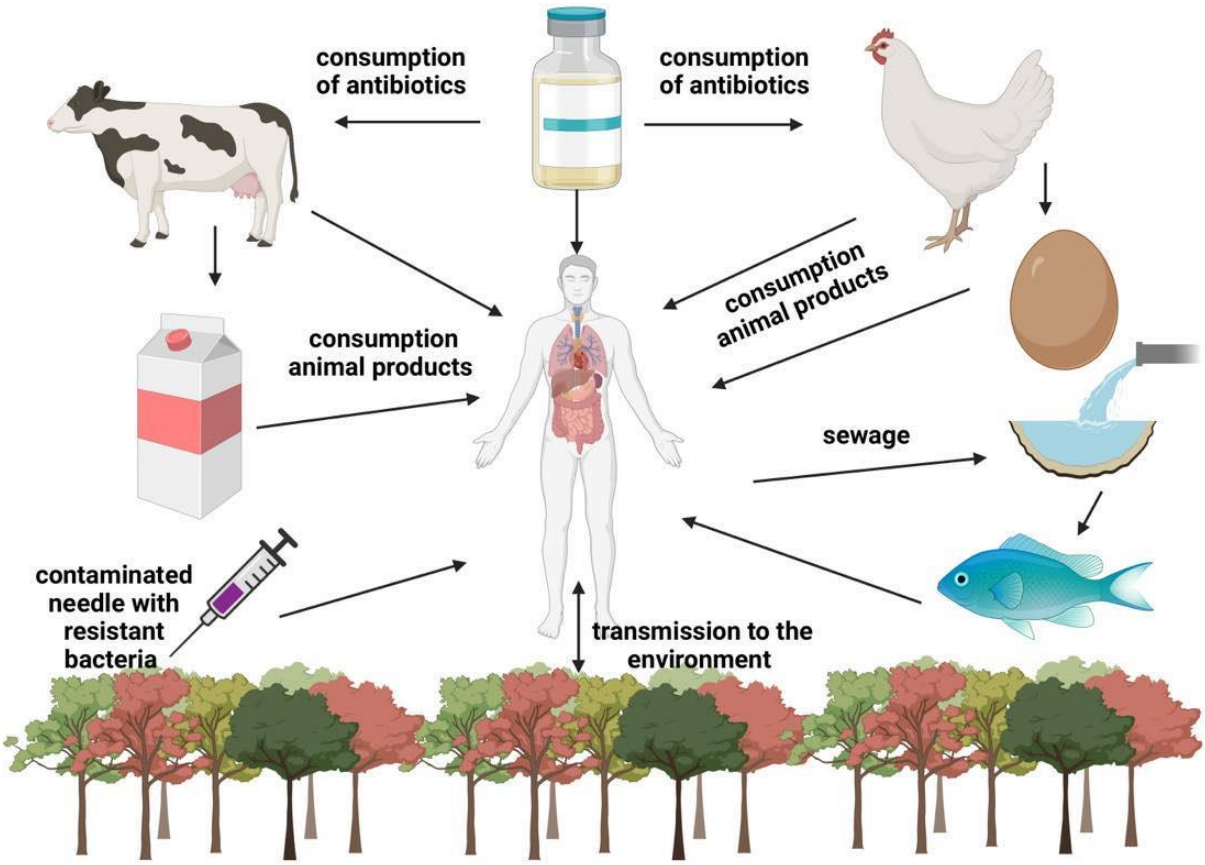

Figure1: The possible routes of transmission of antibiotic resistance to human (created with biorinder with permission) [59].

8. Rules for resistance management

In 2015, the WHO released the "Global Action Plan (GAP) on AMR," which focuses on a set of interventions include immunization and reducing infection prevalence through improved hygiene, sanitation, and steps to avoid infection. Avoiding diseases that are (becoming) incurable due to antibiotics, decreasing the spread of viral infections that may result in secondary bacterial infections requiring antibiotic treatment, and preventing infectious diseases that require excessive antimicrobial medications. Additionally, vaccination can lower the need for antibiotics by reducing the spread of illnesses within the community and boosting herd immunity [60]. In an effort to set regulations to restrict the use of antimicrobials in animals used for food and reserve specific classes, the WHO has also ranked antibiotics according to their value to human medicine [61].

In 2018, Egypt developed its national action plane (NAP) for antimicrobial resistance for the duration from 2018 to 2022 (Egypt National Action Plan for Antimicrobial Resistance, 2018). It set four main objectives: first, improving public awareness of AMU and AMR; second, optimizing the use of antimicrobials in human and animal sectors; third, strengthening the One Health engagement; finally, implementing evidence-based practices for infection prevention and control [62].

The committee of the European Food Safety Authority and the European Medicines Agency proposed certain recommendations to reduce the use of antimicrobial drugs in animal husbandry in the European Union and the impact on food safety [63]. The following concepts were suggested.

1. Establishing national strategies for monitoring antibiotic use and AMR development.

2. Set national targets for antimicrobial use reduction.

3. Applying monitoring programs for checking farm health regularly

4. Veterinarians should be given more authority to prescribe antibiotics.

5. Provide a lot of rapid and reliable diagnostics methods.

6. Strengthen disease prevention and control husbandry and management practices.

7. Reconsider animal production methods to overcome the risk of endemic disease.

The Indian government has restricted the use of prophylactic antibiotics in aquaculture and placed emphasis on the proper implementation procedures. Antibiotic overuse in animals results in the accumulation of antibiotic residues in the food chain. Also, The Indian Council of Medical Research (ICMR) suggested important action points for urgent implementation of antimicrobials use in food animals [64] which include the followings:

1- Fluoroquinolones, colistin, vancomycin, and 4^{th} and 5^{th} generation cephalosporins (carbapenems), which are designated as critically important or last-line antibiotics for human therapy, should not be used to treat animals used for human consumption. Only antibiotics approved for use in treating animals, such as quinolones, aminoglycosides, penicillin, sulphonamides, tetracyclines, and cephalosporins, should be used. Carbapenems and glycopeptides are used to treat pets.

2- Standardization of diagnostic methods: Diagnostic techniques for identifying AMR in animals need to be developed once more for them to be applied consistently in all veterinary laboratories across the country.

3- Research areas: To figure out how resistant isolates spread via fisheries, animals, and people. So, research studies on routes and mechanisms of transmission are required.

In addition to rising resistance to existing agents, The O'Neil commission also looked at ways to combat the worldwide problem of antibiotic resistance. The panel recommended the following suggestions to limit antibiotics [65].

- Launch a large international public awareness effort to educate the public about the antimicrobial resistance crisis.
- Enhance hygiene and stop the spread of infection.
- Limit the overuse of antimicrobials in the environment, especially in the agriculture field.
- Bolster international monitoring of antimicrobial use and medication resistance in both humans and animals.
- Promotes rapid accurate diagnostics techniques to stop the unnecessary use of antibiotics.
- Encourage the development of vaccinations and other alternatives.

9. Alternative methods used for the Control AMR

Scientists are continuously looking for new approaches instead of antibiotics to control and overcome the problem of AMR. Many substitutional regimens were adopted (Figure 2).

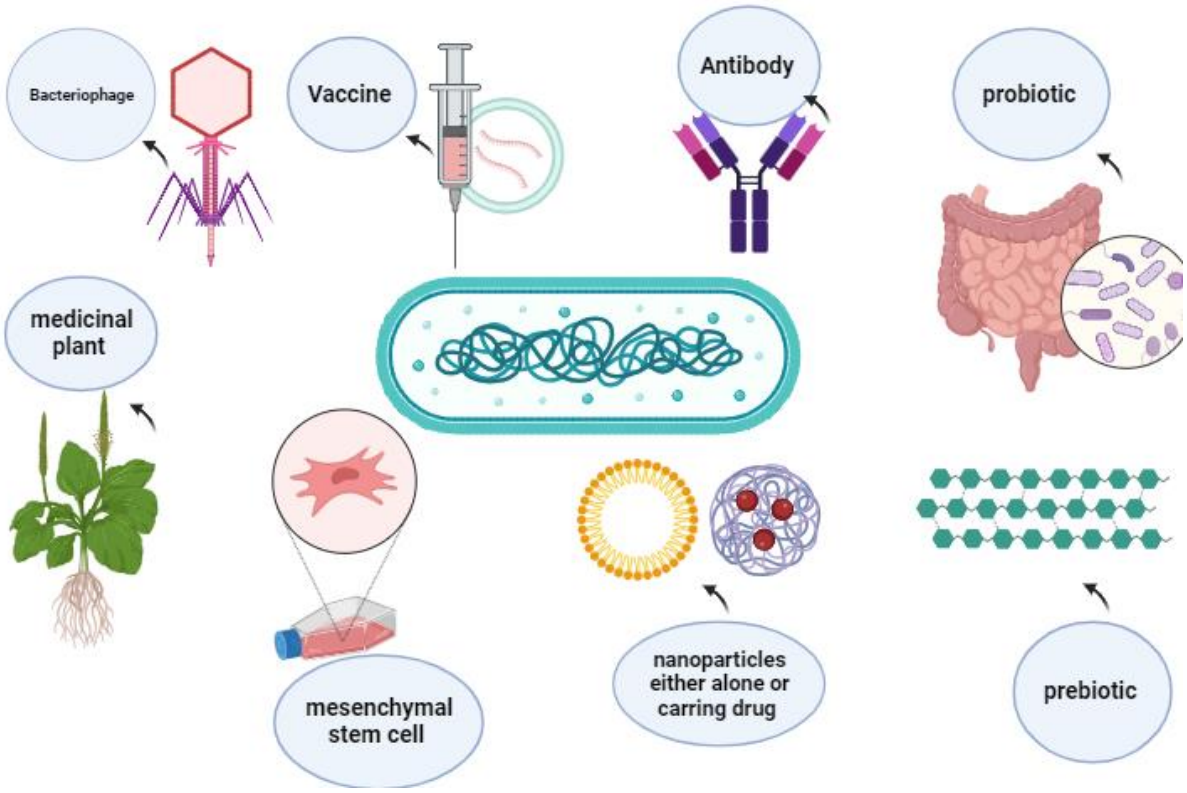

Figure.2: Some alternative methods used instead of antibiotics to fight AMR bacteria in addition to other alternatives that doesn't present in the figure as anti-quorum sensing compounds, antimicrobial proteins, anti-plasmid, and plasmid Figure.2: Some alternative methods used instead of antibiotics to fight AMR bacteria in addition to other alternatives that doesn't present in the figure as anti-quorum sensing compounds, antimicrobial proteins, anti-plasmid, and plasmid curing, CRISPR-Cas system, fecal microbiota transplantation, and physicochemical methods (created with biorinder with permission) [66]

9.1 Phage therapies

A virus that infects bacteria and damages it is called a bacteriophage or phage. Their ability to cause deadly effects specifically and potently in the host bacterium through cell lysis gives them therapeutic potential in medicine to manage MDR pathogens as it targets the bacteria only without affecting the human cells [67]. For the development and reproduction of phage capsids, lipids and proteins are necessary, and they are produced by phages using the host's biosynthetic system [68]. Peptidoglycan hydrolases (PGH), often referred to as virion-associated peptidoglycan hydrolase (VAPGH) or endolysin, are particularly important for the destruction of the bacterium and the discharge of phage particles into the environment when a

phage attacks bacteria [69]. Because they specifically target conserved structural components of bacteria. In comparison to antibiotics, phage-derived lytic proteins have several benefits, such as (a) quick and widespread bactericidal activity on the target pathogen, (b) absence of resistance development, and (c) harmonious action with other antibiotics or lysins [70]. Typhoid fever and *S. aureus* bacteremia have both been demonstrated to respond favorably to phage therapy [71].

9.3Antibodies

Monoclonal antibodies, or mAbs, are primarily used to treat rheumatoid arthritis, psoriasis, multiple sclerosis, cancer, and immunological deficiencies. Clinical trials on a variety of antibodies are being conducted for bacterial infections. However, only three antibodies have been given the go-ahead to be used in the limitation of some bacterial infections [72].

The primary modes of action of mAbs differ from those of traditional small-molecule antibiotics, and they also present a decreased threat of the emergence of drug resistance. Bactericidal mechanisms and anti-virulence mechanisms are two categories into which they can be separated. The host's innate and adaptive immune defense mechanisms are aided by the inhibition of bacterial virulence pathways, which also limits collateral harm like the emergence of drug resistance. Toxin neutralization has proven to be the most successful strategy [73].

In 2015 Lehar et al stated that an antibody-antibiotic combination has been demonstrated to kill intracellular *S. aureus 01*, and this conjugation was found to be more effective than vancomycin for the treatment of bacteremia [74]. Antibodies combined with photodynamic therapy show satisfied results in destroying different MRSA strains, in their growth phases and may be an excellent candidate for a new method of treating MRSA infections [75].

9.4 Anti quorum sensing compounds

A bacterial communication method called quorum sensing (QS) is used to coordinate group behaviors in a way that depends on cell density. One of virulence weapons is that pathogens can change their transcription patterns to an invasive phenotype at high concentrations, including genes associated with antibiotic tolerance and virulence determinants, and then spread disease [76]. Anti QS works by stopping the spread of disease by blocking cell-to-cell interaction, giving the immune system the ability to stop the invasive pathogen and get rid of an infection that already exists. Instead of killing the bacteria, an antibiotic approach is employed to reduce their pathogenicity [77].

9.5 Antimicrobial Proteins

Antimicrobial peptides (AMPs) are tiny proteins which are considered the first line of defense against pathogens. They have been extracted from plenty of natural sources, including microorganisms, insects, plants, animals, crustaceans, and people. It has been found that several drug-resistant strains can be inhibited when combined with several AMPs and traditional antibiotics. a result of a synergistic impact. In comparison to natural AMPs, synthesized AMPs are more potent, less toxic, and more protease-resistant [78]. Once some AMPs break down the cell wall, they continue to apply their antimicrobial effects by concentrating on protein biosynthesis, nucleic acids, and/or reducing the development of cell walls

and membranes [79]. In the case of Enterococci, the conjugation of AMP magainin with vancomycin produced very promising results [80].

9.5.1 Bacteriocins

Bacteriocins, which are defined as antimicrobial peptides with a variety of modes of action and activities that are also safe for humans, are produced by almost all bacterial species. Bacteriocins may eventually replace antibiotics in the treatment of MDR infections [81]. There are three different bacteriocins (nisin A, lacticin Q, and nukacin ISK-1) have efficacy against MRSA biofilms by forming pores and causing degradation of the cell wall of the target bacteria [82].

It was found that MRSA, and *Clostridium difficile* have been successfully treated with the bactericide Bacteriocin Duracin 61A, which has synergistic benefits when paired with reuterin or vancomycin [83].

9.5.1 Stem Cell-Derived Antimicrobial Peptides

To offer a safe and effective therapeutic option against a number of chronic diseases, mesenchymal stem cells (MSCs) have been the focus of extensive study for many years [84]. Mesenchymal stem cells (MSCs) may be able to aid in tissue healing, immunomodulation, and the control of excessive inflammation. According to recent studies, human MSCs create compounds known as antimicrobial peptides (AMPs), which can block the production of bacterial cell walls among other methods of bacterial killing [85].

9.6. Probiotics, prebiotics and synbiotics

Probiotics are now defined by the WHO as "live microorganisms which, when supplied in adequate amounts, provide beneficial health effects to the host" [86]. The commonly used probiotic microorganisms are several bacteria belonging to the genera *Pediococcus, Lactococcus, Enterococcus, Streptococcus, Propionibacterium,* and *Bacillus* [87]. The health benefits of probiotics are associated with preventing and reducing many diseases, i.e., allergic diseases, cancer, hypercholesterolemia, lactose intolerance, inflammatory bowel disease, diarrhea, and irritable bowel syndrome [88]. Probiotics work by i) producing chemicals that interfere with the growth of other pathogenic microorganisms, such as bacteriocins, organic acids, and H2O2; ii) preventing pathogenic microorganisms from attaching to surfaces; iii) battling hazardous microorganisms for food; iv) blocking toxin receptors, degrading the poisons, and v) controlling immunological reactions [89].

Probiotics have the capacity to assist the body in developing a layer of intestinal mucosa more healthy and protective, boosting the intestinal barrier integrity, and subsequently enhancing immunity [90]. Probiotics assist in avoiding infection through a range of unique process, such as competition for ecological resources, colonization resistance, and nutrition, as well as the synthesis of AMPs with bactericidal activity [91].

Prebiotics are a kind of nutrient that are broken down by the gut microbiota and have beneficial effects on human health. The two main prebiotic groups are galacto- and fructo-oligosaccharides, and their breakdown products are short-chain fatty acids that are released into the bloodstream [92].

Prebiotics like inulin and pectin have been shown to provide several health benefits, including a decrease in the

frequency and length of diarrhea, relief from inflammation and other intestinal bowel problem symptoms, and preventive actions against colon cancer [93]. They are also thought to reduce several risk factors for cardiovascular disease, increase the bioavailability and uptake of minerals, and promote satiety and weight loss, which helps to prevent obesity [94]. Prebiotics act via enhancing the function of the intestinal barrier, lowering the number of harmful bacteria, and producing short-chain fatty acids, or SCFAs [95].

Prebiotics and probiotics are combined to create synbiotics, which are utilized to improve both human and animal health [87]. Either probiotics or prebiotics were used to maintain gut microenvironment healthy through several methods such as competitive inhibition, and production of specific compounds such as SCFA, organic acids, etc.; and modulation of the immune system for better cellular growth and eradication of infections all of these resulting in healthy intestine with powerful immunity [96].

9.7. Anti-Plasmid and plasmid curing

Plasmid is a very small circle double strands of DNA that transfer information from cell to another. The innovative method of eradicating plasmids from bacterial populations is an effective means of preventing AMR. The possibility of developing treatments for both humans and animals, particularly those used for food production, makes research in this field urgently necessary. New anti-plasmid and plasmid cure techniques are therefore a potentially useful tool to lower the frequency of AMR genes. Other methods, from a One Health standpoint, consider curing plasmids in environmentally active areas, like wastewater or agricultural settings [97]

9.8. CRISPR-Cas System

The CRISPR-Cas (clustered regularly interspersed short palindromic repeats-CRISPR associated protein) adaptive immune system of bacteria employs DNA-encoded, RNA-mediated, or DNA-targeting processes that hinder the attack of bacteria by mobile genetic elements such as phages and plasmids and other foreign genetic material [98]. With the help of these gene-editing technologies, it is possible to target bacterial genomes quantitatively, specifically, and selectively to diminish or completely eradicate antibiotic resistance and open up new therapeutic avenues for MDR illnesses [99].

9.9. Nanoparticles

Nanotechnology is an interesting field in science, with many possible applications in medicine. It concerns the synthesis and characterization of atoms. It can solve a wide range of problems regarding the wellbeing and productivity of animals. Nano systems come in many forms including polymer-coated nanocrystals, metallic nanoparticles, polymeric nanospheres, carbon nanotubes, nano shells, liposomes, and dendrimers. By improving therapeutic efficacy and minimizing side effects, the creation of antimicrobials in nanoparticle systems is recognized as an excellent alternative antimicrobial delivery technique for treating microbial infections [100].

Nanoparticles are distinct from their larger-sized counterparts in terms of their physical, chemical, and biological properties. A greater surface area in ratio to volume, improved mechanical strength, and enhanced chemical reactivity or

stability are the causes of this impact [101]. According to Khan *et al*, NPs can be categorized into many classes according to their sizes, shapes, or physical and chemical characteristics. This is because of their high surface area and nanoscale size, which give them unique physical and chemical capabilities. Ceramic NPs, metal NPs, and polymeric NPs are a few of the various groups [102].

Nanoparticles may exhibit antibacterial activity through a variety of mechanisms, including: (1) interaction with the cell wall of the bacteria and disrupt it; (2) prevention biofilm formation; (3) stimulate the innate and adaptive immune responses of the host; (4) release of reactive oxygen compounds (ROS); and (5) induction of intracellular effects (e.g., interactions with DNA and/or proteins). Because they do not present the same mechanisms of action of standard antibiotics, they can be of extreme use against MDR bacteria [103]. Nanoparticles such as liposomes, polymeric, magnetic, silica, and gold NPs were used to as MDR inhibitors through increasing drug efflux altered metabolism, activating DNA repair, and changing apoptotic pathways [104].

In the scientific field of pharmacology, nanoparticles are regarded as the best medicine delivery technology because they not only protect animals against bacterial or viral infections but also speed up wound healing and lessen discomfort. These novel chemicals also facilitate medicine delivery to the organs and tissues that need it. They alter how drugs or other substances are absorbed, utilized, digested, and expelled from the body, acquiring a therapeutic effect, enhancing bioavailability, stability, lengthening movement, and reducing the frequency of doses necessary to maintain therapeutic responses and toxicity [105].

9.10. Medicinal plants

Some medicinal plants of genera Euclea, Ficus, Aloe, Lippia, and A rtemisia offer promising solutions towards overcoming multi-drug resistance [106]. Plant extracts, also known as photobiotics, have been found to have activity against bacterial, antioxidant and anti-inflammatory properties [107]. The derived antibacterial ingredient from these plants may inhibit bacterial, fungal, virus, and protozoal growth by different mechanisms than those of currently employed antimicrobials, making them potentially helpful in treating resistant microbial strains [108]. Alkaloids prevent growth of the bacteria via suppression of bacterial nucleic acid replication and protein synthesis, alteration of the permeability of bacterial cell membranes, bacterial cell membrane and cell wall damage, suppression of bacterial metabolism, and suppression of efflux pumps [109]. Flavonoids can modify cell membranes and hinder several processes including nucleic acid production, cytoplasmic membrane function, energy metabolism, attachment and biofilm development [110]. The ability of tannins to penetrate the bacterial cell wall to the interior membrane, interfere with the metabolism of the cell, and ultimately cause the cell's demise account for their antibacterial activity [111]. Tannic acid prevents bacteria from adhering to surfaces, which causes bacterium cell death. In addition, tannic acid prevents bacteria from absorbing sugar and amino acids, which restricts their ability to develop [112].

Essential oils (EOs) are natural, aromatic liquids that are created by plants to defend themselves against a variety of pathogenic bacteria. They can be collected from a variety of components of medicinal plants, particularly the leaves

and flowers. Due to their antibacterial properties, EOs have undergone substantial research to determine whether they may be utilized to treat a variety of microbial illnesses [113]. The efficacy of EOs resulting from they might attach to the surface of the cell, and then penetrate the cell membrane and after accumulation, disruption to the integrity of membrane occurs, which can detrimentally influence the cell metabolism causing cell death [114]. Black pepper essential oil (BPEO) causes death of bacterial cell by breaking cell membrane and leakage of the internal contents. Therefore, BPEO-treated *E. coli* developed deformities, pits, and shriveled [115]. Some EOs have shown antimicrobial activity against *L. monocytogenes*, *E. coli*, *Bacillus thermosphacta*, and *Pseudomonas fluorescens* [116].

9.11. Fecal microbiota transplantation (FMT)

The technique of Fecal microbiota transplantation (FMT) is another replaced method that shows hope in the fight against AMR. The patient's unbalanced gut microbiota is restored through the delivery of fresh, frozen, or encapsulated fecal matter from a qualified donor. According to randomized clinical trials, the FMT method is over 90% effective at treating recurrent *Clostridium difficile* infections [117]. The FMT method is also effective for treating vancomycin-resistant Enterococci when it predominates over the rest of the gut microbiota and when *C. difficile* is present [118].

9.12. Physicochemical methods

Atmospheric pressure non thermal plasma (APNTP) is a new method that is being studied for its antibacterial properties [119]. Although the precise processes of APNTP-mediated bacterial inactivation remain unknown, it is believed to be effective through produced products such UV radiation, reactive nitrogen species (RNS), reactive oxygen species (ROS), and charged particles inside a plasma gas phase [120]. The following ROS are thought to be involved in the inactivation of bacteria: peroxide, superoxide, atomic oxygen, ozone, singlet oxygen, and hydroxyl radicals [121]. These processes function primarily through the oxidative damage UV radiation causes to nucleic acids, lipid peroxidation brought on by ROS, which mostly affects fatty acids close to the cell surface, and the chemical alteration and destruction of proteins, which is primarily brought on by hydroxyl radicals. According to other investigations, ROS may have caused apoptosis in bacterial cells [122].

Sonodynamic antimicrobial chemotherapy has a unique mechanism depends on the cooperative effect of ultrasound and a substance known as "sonosensitizer" (SS) [123]. As it was found that the inaudible sound with a frequency not more than 20 kHz is able to kill many microorganisms [124].

9.13. Vaccines

Vaccine is an important method to cease the incidence of virus or bacterial infection in humans and animals. As it reduces the consumption of antibiotics resulting in reducing or preventing the occurrence and spread of resistant pathogens. They play a direct and indirect role in the battle against AMR. Directly by reducing the risk of infection and, indirectly, by preventing the spread of resistant strains to other non-resistant species, vaccines have an impact on resistant infections. Lessening the prescription of needless antibiotics and

lowering the likelihood of superinfections and secondary infections that would necessitate taking high doses of antibiotics are two factors that contribute to a drop in the incidence of infections [125]. Vaccines are also accountable for the absolute eradication of rubella, tetanus, diphtheria, pertussis, mumps, measles, and poliomyelitis [126]. There are many types of vaccines used today including: live attenuated vaccines (LAV), inactivated bacterial pathogens, toxoid and subunit vaccines [127].

Live Attenuated vaccines are more powerful strategy particularly against intracellular infections than inactivated vaccines. They are defined as pathogenic microorganisms that have lost their virulence but retain the ability to transiently replicate intracellularly. Developing bacteria (or viruses) under abnormal circumstances for an extended period can typically result in pathogenicity loss. This results in mutants that replicate more efficiently under these artificial conditions than in a natural host. An example of this vaccine is *Mycobacterium bovis* strain *Bacillus Calmette–Guerin (BCG*) [128].

To produce a vaccine, the pathogen must be heated or chemically treated. The inactivation processes destroy the pathogen's ability to replicate but maintain it "intact" so that the immune cells can recognize it easily. It was discovered that inactivated vaccinations frequently need booster shots to produce long-lasting immunity and frequently offer a shorter duration of protection than live vaccines [129]. An example of a killed vaccination is the cholera vaccine, which contains dead *Vibrio cholera (V. cholera)* [130].

Toxoid vaccines are made up of exotoxins that have been chemically or genetically inactivated and are produced by a variety of bacteria, including *C. tetani, Yersinia pestis, V. cholerae, C. diphtheriae, Bacillus anthracis, Shigella dysenteriae, C. botulinum, E. coli, S. aureus,* and *rickettsia*. When the A subunits of *S. dysenteriae toxin (STA)* and diphtheria toxin (DTA) are picked by receptor-mediated mechanisms, they restrain the synthesis of cellular protein in a unique way, which results in cell death [131].

Conclusion

In nations where the use of antibiotics is still authorized and overused in the breeding of livestock, discovering approaches that are equally effective as current therapies can bring about good changes. Antibiotics must not be promoted unethically, and measures to prevent their excessive or inappropriate usage must be taken. Many novel pathways are now being investigated with the aim of combating present and emerging resistance, albeit it will take many years before we will be able to establish their utility. Several innovative techniques have been developed to increase antibiotic efficacy through novel targets. physicochemical methods, antimicrobial peptides, medicinal plant, bacteriophage, probiotics, synobiotics, prebiotics, fecal transplants, and nanoparticles are alternative approaches that may become promising methods to enhance both human and animal health and decrease the unnecessary use of antibiotics. Governments, institutions, and regulatory agencies should work together to develop innovative strategies for enhancing antibiotic efficacy through novel targets.

Conflict of Interest

The authors have no conflict to declare.

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الملخص العربى
الاستراتيجيات البديلة الممكنة لمكافحة مقاومة مضادات الميكروبات

السيد أحمد عبد العزيز, سوسن محمد على الشيخ, عزه جلال , يمنى رفقى*
قسم الفارماكولوجي , كلية الطب البيطري, جامعة الزقازيق, الزقازيق
44511, مصر

تعتبر المضادات الحيوية أحد أهم اكتشافات القرن العشرين. لكن الكائنات الحية الدقيقة المقاومة للمضادات الحيوية تظهر بسرعة عندما يستخدم البشر والحيوانات المضادات الحيوية بلا مبالاة. ومن المؤسف أن مقاومة المضادات الحيوية اكتسبت أهمية دولية في السنوات الأخيرة باعتبارها السبب الرئيسي للوفاة والكارثة الاقتصادية في جميع أنحاء العالم. هناك حاجة ملحة إلى إيجاد وإنشاء تقنيات مبتكرة لمعالجة مقاومة المضادات الحيوية. لا يمكن حل تحدي مقاومة المضادات الحيوية عن طريق الأدوية الجديدة وحدها. تسلط هذه المقالة الضوء على أسباب وآليات مقاومة مضادات الميكروبات والآثار الضارة الناجمة عن انتشارها على نطاق واسع. بالإضافة إلى ذلك، فإنه يركز على الأساليب الجديدة الأخرى التي قد تظهر فعاليتها في السيطرة على مقاومة مضادات الميكروبات ومكافحتها، بما في ذلك بعض الطرق الفيزيائية والكيميائية، والببتيدات المضادة للميكروبات، والنباتات الطبية، والعاثيات البكتيرية، والبروبيوتيك، والسينوبيوتيك، والبريبايوتكس، نقل جراثيم البراز، والجسيمات النانوية. قد تصبح هذه الأساليب البديلة طرقًا واعدة لتعزيز صحة الإنسان والحيوان وتقليل الاستخدام غير الضروري للمضادات الحيوية. وينبغي للحكومات والمؤسسات والهيئات التنظيمية أن تعمل معا لتطوير استراتيجيات مبتكرة لتعزيز فعالية المضادات الحيوية من خلال أهداف جديدة.