Review

Combating Antibiotic Resistance in a One Health Context: A Plethora of Frontiers

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Combating Antibiotic Resistance in a One Health Context: A Plethora of Frontiers

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Abstract: One of the most significant medical advancements of the 20th century was the discovery of antibiotics, which continue to play a vital tool in the treatment and prevention of diseases in humans and animals. However, the imprudent use of antibiotics in all fields of One-Health and concerns about antibiotic resistance among bacterial pathogens have raised interest in antibiotic use restrictions on a global scale. Despite the failure of conventional antimicrobial agents, only about 15 new antibiotics have been introduced clinically since year 2000 to date. Moreover, there have been reports of resistance to some of these new antibiotics. This has necessitated a need to search for an alternative strategy to combat antimicrobial resistant pathogens. Thus, this review compiles and evaluates the approaches—natural compounds, phage treatment, and nanomaterials—that are being used and/or suggested as the potential substitutes for conventional antibiotics. These strategies include those that focus on the enzymes or proteins, as well as the physiology and metabolism of resistant bacteria.

Keywords: Alternative therapy; antimicrobial resistance; natural product/compound; One-Health; secondary metabolite

Introduction

Antibiotics are used for a variety of reasons, including the ordinary support of human health and growth, the stimulation of growth in food-producing animals, which is not a therapeutic application—and the prevention of disease, which accounts for a large portion of antibiotic use in both humans and animals (Allen et al., 2014, Ajose et al., 2022a). Antibiotics have traditionally been regarded as the first line of defense in the treatment of bacterial diseases in animal husbandry. They have also prevented innumerable deaths and allowed for the advancement of modern medicine for many years (Czaplewski et al., 2016). However, their misuse and overuse have led to the development of antimicrobial resistance (AMR) in most of pathogenic bacteria. Bacterial resistance development is a persistent phenomenon that frequently renders even last-resort antibiotics ineffective. The lack of progress in the development of new antibacterial medications and the evolution of antibiotic resistance to practically all currently available antibiotics are factors in the global health crisis (Solomon and Oliver, 2014). In recent years, infectious diseases caused by bacteria have become serious and more prevalent in clinical settings, placing a serious economic burden and a threat to public health (de Kraker et al., 2016). According to McLinden et al. (2014), bacterial infections are thought to be responsible for at least half of all the economic costs of all foodborne diseases in the United States, which range from $10 to 83 billion yearly. This report was corroborated by Hoffmann et al. (2015). The spread of genes that confer antibiotic resistance among bacteria is aggravating the problem of antibiotic resistance (Peterson and Kaur, 2018). The acquisition of

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antibiotic resistance genes (ARGs) by the bacteria, may lead to treatment failure and morbidity and mortality rates in humans (San Millan, 2018).

Antibiotic resistance is a worldwide problem that is causing increasing public health concerns, and it is now recognized as a crucial One-Health issue (Ajose et al., 2022b). When contemplating potential interventions to mitigate or preempt this problem, it is imperative to elucidate the intricate elements that have contributed to the development of bacterial antibiotic resistance. Over 80 years of antibiotic use have put pressure on bacteria to evolve specialized mobile ARGs, especially in pathogenic bacteria. These AMR organisms in environmental "hot spots" translocated the phenomena of resistance to related species (Adhikari et al., 2022, Larsson and Flach, 2022) (Figure 1). Bacteria and their genetic material (DNA and/or plasmids) can be easily transmitted between humans, animals and/or environment (Figure 1). As a result, AMR is dangerous and is characterized by intricate interactions between various microbial populations that affect human, animal, and environmental health (WHO, 2015, Robbins et al., 2016). In light of this, measures made (or not done) to counteract AMR in one division may have an effect on other divisions.

The primary impact of AMR is the large rise in the risk of disease transmission, life-threatening illness, and death as antimicrobials lose their effectiveness and make infections harder to cure. AMR is noteworthy since it appears in all different forms (Murugaiyan et al., 2022). Notably, COVID-19 pandemic has accelerated the spread of MDR bacteria as a result of the overuse and abuse of currently available antibiotics as well as other antibiotic resistance-promoting factors (Manohar et al., 2020, Pelfrene et al., 2021) (Figure 2). Multidrug resistant (MDR) pathogens are becoming a major worldwide health problem because they have an impact on infection identification, treatment, and prevention. However, organisms that are extensively drug-resistant (XDR) and pan-resistant (PDR), which are practically intractable with conventional therapy, are of paramount concern (Murugaiyan et al., 2022). Since even so-called "antibiotics of last resort" are becoming ineffective, new strategies are being applied to prevent and cure MDR, XDR, and PDR infections in light of the impact AMR bacteria have on the world's health and the need for new antibiotics (Mulani et al., 2019).

Louis Pasteur made groundbreaking discoveries in the fields of immunology, vaccinology, and microbiology that changed clinical science and save millions of deaths. Due to recently developed tools and infection models, our capacity to study infectious disease has experienced significant modifications since the 19th century. We saw a tremendous desire to comprehend the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and to develop potent disease-prevention vaccines during the COVID-19 pandemic. We need to discover new or alternative strategies to tackle antibiotic-resistant bacterial strains that cause millions of deaths every year with the same haste that we did for the comparatively underappreciated AMR pandemic (Mostowy, 2022). Future advances in disease prevention or treatment will determine how successful humanity remains. The spread of ARGs among pathogenic bacteria raises concerns about the continued effectiveness of the current antibiotic arsenal (Allen et al., 2014).

It might be prudent to think about the possibilities of non-traditional techniques given the emergence of antibiotic resistance and the difficulties in discovering and developing conventional antibiotics, which have resulted in a very short pipeline of new medicines. Utilizing antibiotic alternatives seeks to improve and promote health and reduce antibiotic overuse. Hence, reducing the selective pressure that leads to the establishment and spread of ARGs. Thus, various alternative strategies in the following categories will be fully highlighted in this review:

a) antimicrobial peptides (AMPs);
b) bacteriophages;
c) nanotechnology;
d) ethno-medicine; and
e) probiotics and prebiotics

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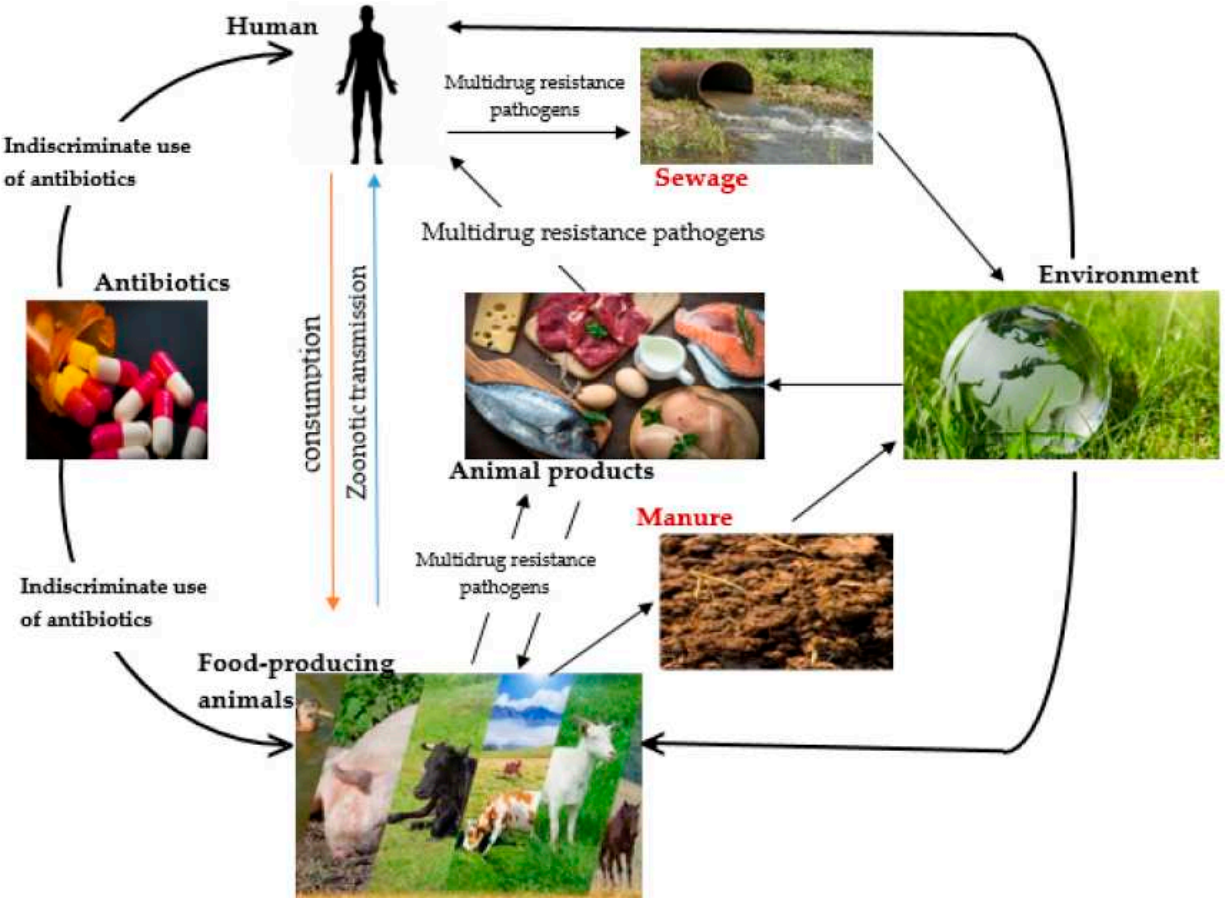

Figure 1. Transmission routes of AMR bacteria between human, animal and the environment Adapted from: (Ajose et al., 2022b).

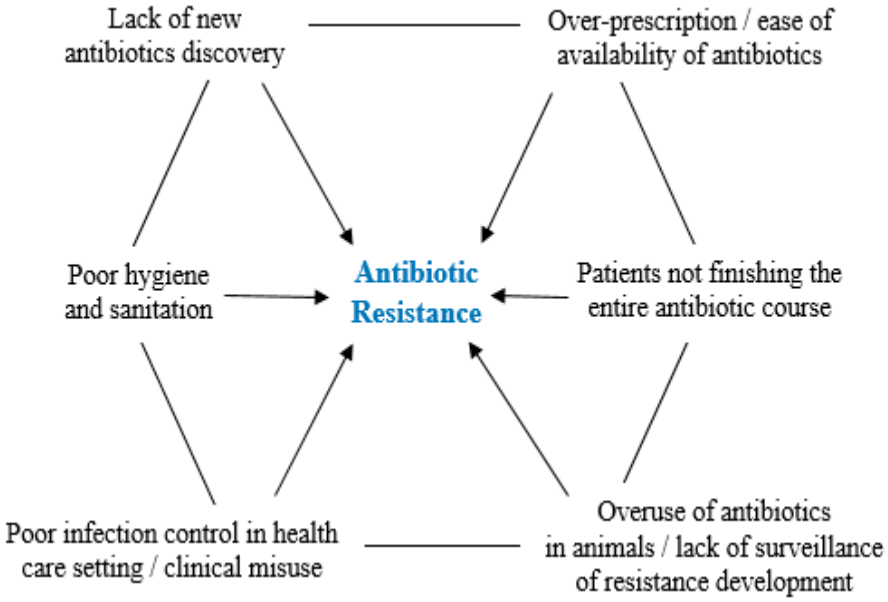

Figure 2. Variables that contribute to antibiotic resistance.

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Mode of Action of Antibiotics and Emergence of Antibiotic Resistance

Antibiotics are categorized into classes based on the class of molecules they include and their targets and principal modes of action (Table 1). Antimicrobial targets include cell membranes, cell walls, protein synthesis, DNA or RNA synthesis, and the creation of biological metabolic compounds.

The overuse and abuse of antibiotics in the human, veterinary, and agricultural sectors has put a lot of pressure on the selection process, leading to an increase in antibiotic resistance in bacteria (Murugaiyan et al., 2022) (Figure 3). This pressure is exerted through a number of mechanisms (Table 1), some of which are either emerging or ancestrally intrinsic to the biology of a pathogen. Some of the mechanisms of bacterial AMR include the following: (1) Enzymatic degradation of antibiotics, such as the bacterial production of beta-lactamases that break down the beta-lactam class of antibiotics; (2) Modification of the antibiotic target, where the target is altered so that the antibiotic can no longer bind to its site of action; (3) Control of drug entry through mutations in bacterial cell wall porin molecules and membrane modifications; (4) The turning on of efflux pump systems, which are able to pump antibiotics outside of the cell before they interact with their targets Figure 4.

Table 1. Mode of action of antibiotics and mechanisms of bacterial antibiotic resistance.

Antibiotic family	Mode of action	Mechanism of resistance	Reference
β-lactams	Cell wall synthesis inhibitors. Binds trans peptidase also known as penicillin binding proteins (PBPs) that help form peptidoglycan	Beta-lactamase production primarily - *bla* genes Expression of alternative PBPs	(Dowling et al., 2017, Tooke et al., 2019, Ibrahim et al., 2019)
β-lactamase inhibitors	Inactivates the enzyme; beta-lactamase Hydrolysis of the beta-lactam ring	Production of extended spectrum beta-lactamases (ESBLs)	
Fluoroquinolones	Binds DNA-gyrase or topoisomerase II and topoisomerase IV; enzymes needed for supercoiling, replication and separation of circular bacterial DNA.	Target modification Decreased membrane permeability Efflux pumps	(Correia et al., 2017)
Macrolides, Lincosamides and Streptogamin (MLS)	Binds the bacterial 50S ribosomal subunits; inhibit protein synthesis	Target site modification Active drug efflux	(Patel and Hashmi, 2021)
Aminoglycosides		Target site modification (via the action of 16S rRNA	(Wendlandt et al., 2013)

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	Bind to the bacterial 30S ribosomal subunit thus inhibit bacterial protein synthesis	methyltransferases (RMTs)) Enzymatic Drug Modification (adenylation, acetylation and phosphorylation), Efflux systems	(Nguyen et al., 2014, Shin et al., 2015)
Tetracycline	Bind reversibly to the 30S ribosomal subunit as such blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex	Efflux systems, Target modification, Inactivating enzymes, Ribosomal protection	(Davis, 2018, Jiang et al., 2019)
Sulfonamides (Folate pathway inhibitors)	Inhibit the bacterial enzyme dihydropteroate synthetase (DPS) in the folic acid pathway, thereby blocking bacterial nucleic acid synthesis	Excessive bacterial production of dihydrofolate reductase (DHFR) Reduction in the ability of the drug to penetrate the bacterial cell wall Production of altered forms of the dihydropteroate synthetase (DPS) enzyme with a lower affinity for sulfonamides Hyperproduction of para-amino benzoic acid (PABA), which overcomes the competitive substitution of the sulfonamides	

Adapted from: (Ajose et al., 2022b).

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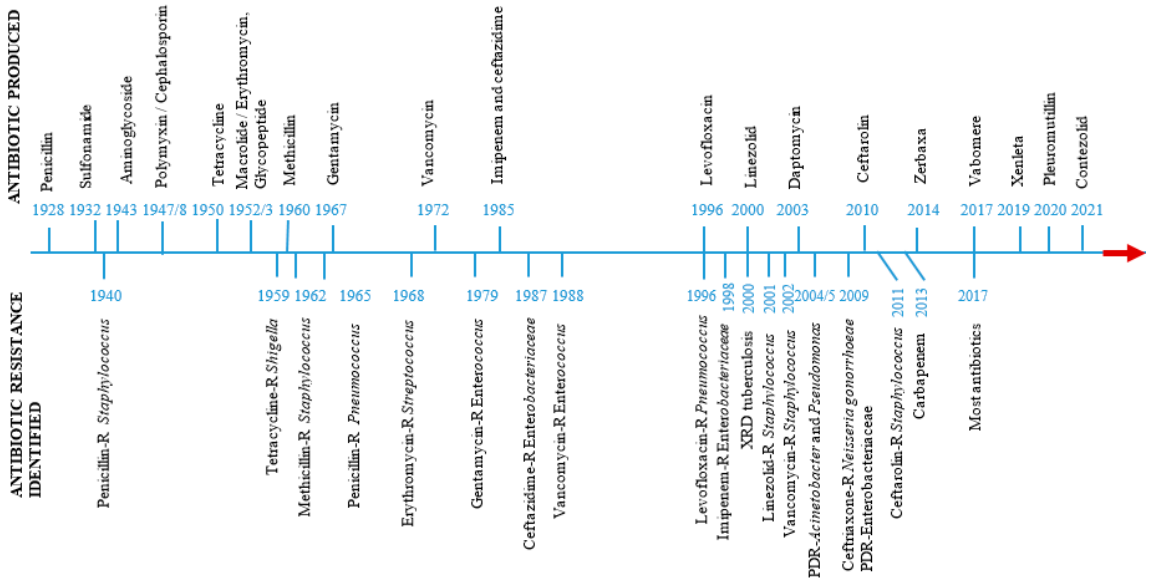

Figure 3. Timeline showing the discovery of antibiotics and the rise of antibiotic resistance over the course of eight decades. XDR – Extensive-drug resistant, PDR – Pan-drug resistant.

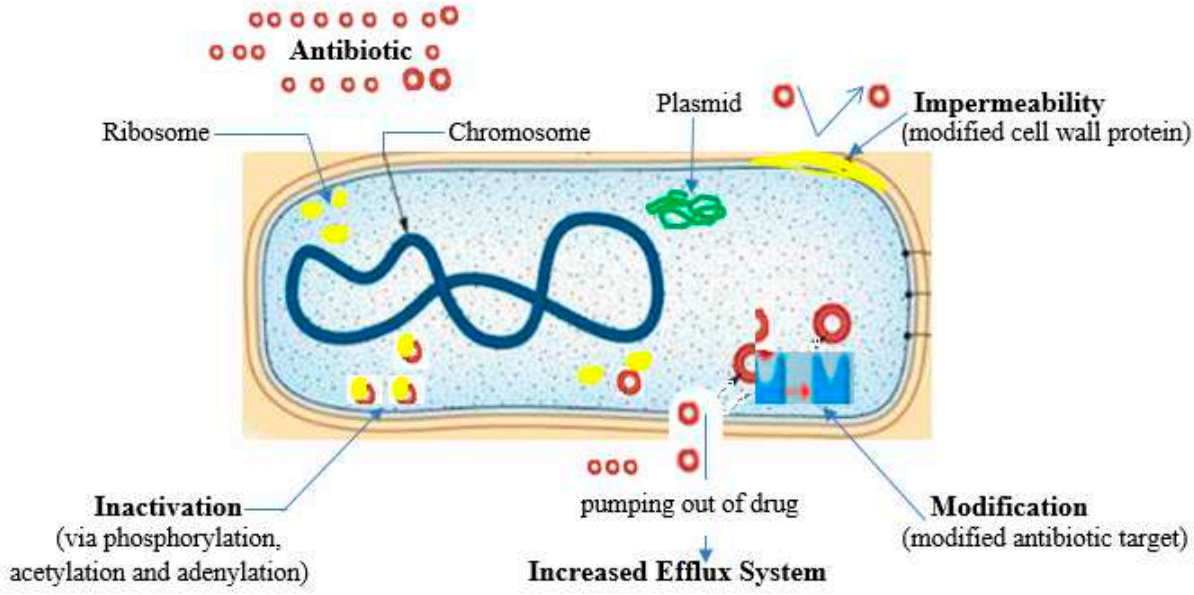

Figure 4. Mechanisms of antimicrobial resistance in bacteria cells.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are a class of tiny molecular peptides that are integral to the innate immune response of the host organism (Wang et al., 2019). They have a critical function in defending against a diverse array of pathogens, encompassing bacteria, fungi, parasites, and viruses (Mohammed et al., 2017, Kang et al., 2017, Lei et al., 2019). The use of AMPs is one of the methods for developing new antibiotics (Zharkova et al., 2019, Dijksteel et al., 2021). When compared to conventional antibiotics, AMPs found in nature have equivalent or even better antibacterial action (Tilocca et al., 2019). They are amphipathic in nature, thus thought to make it easier for the negatively charged bacterial membranes to interact electrostatically, which would then disrupt the lipid bilayer

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structure (Yeaman and Yount, 2003). Their size from 10 to 50 amino acids, and have an overall cationic charge (Sheard et al., 2019). AMPs are present everywhere to include mammals, amphibians, microorganisms and insects and in a variety of natural settings including the oceans (Huan et al., 2020). Through the similar mechanisms of conventional antibiotics, AMPs can target both Gram-positive and Gram-negative bacteria (Sheard et al., 2019, Rima et al., 2021). Once AMPs have penetrated the bacterial cell wall, they continue to act as an antibacterial agent by concentrating on protein biosynthesis, nucleic acids, and/or affecting membrane and cell wall formation (Nguyen et al., 2011, Le et al., 2017, Łoboda et al., 2018).

Antimicrobial Peptide Mode of Action

AMPs are receiving more attention, and new biophysical approaches are continually being developed, although the precise details of their molecular mechanism of action are still not fully understood. In bacteria with negatively charged surface layers made up of lipids like phosphatidylglycerol (PG), cardiolipin (CL), and lipopolysaccharides (LPS), or lipoteichoic acid (LTA) in positively charged surface bacteria, the combination of cationic and hydrophobic residues promotes a strong electrostatic interaction (Molchanova et al., 2017). Additionally, folding of the AMPs caused by hydrophobic contact with bacterial envelopes is what gives these peptides their antibacterial effects. The significant quantity of neutral phosphatidylcholine / cholesterol / sphingomyelin lipids gives mammalian cell membranes a zwitterionic surface, which results in a reduced attraction between cationic peptides and host cells. This is the source of the cell selectivity seen for many AMPs. Since AMPs impair the integrity of bacterial membranes, causing leakage of cell content and subsequent cell death, it is believed that the bacterial membrane is the primary target for AMPs (Torcato et al., 2013, Łojewska and Sakowicz, 2021). Models of AMP disruption of bacterial membranes have been described (Yeaman and Yount, 2003), and they include the carpet model (Shai and Oren, 2001), aggregation (Wu et al., 1999), molecular electroporation (Miteva et al., 1999), toroidal hole development (Hof et al., 2001), sinking raft (Pokorny et al., 2002), barrel-stave model (Huang, 2000), interfacial activity (Wimley, 2010), and lipocentric pore formation (Fuertes et al., 2011). Although the bacterial membrane is the primary target of AMP, intracellular targets including protein synthesis (indolicidin), nucleic acid synthesis (buforin II), RNA synthesis (Bac5 and Bac7), enzymatic activity (pyrrhocoricin), ATP efflux (histatins), or cell wall synthesis (nisin) have also been reported (Nguyen et al., 2011, Pasupuleti et al., 2012) (Figure 5).

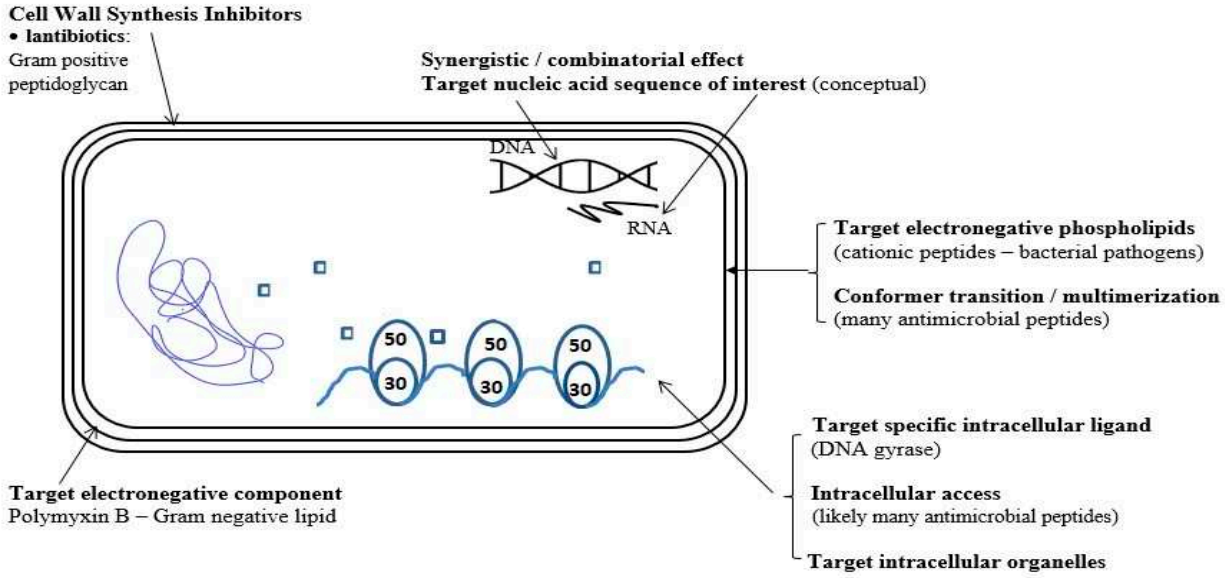

Figure 5. Antimicrobial peptides mechanisms of action.

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Antimicrobial Peptides as Therapeutic Agents

The attributes that make AMPs ideal therapeutic candidates include broad-spectrum antibacterial activity against MDR pathogens, quick onset of killing, and a relatively low chance of resistance development (Sheard et al., 2019, Rima et al., 2021, Łojewska and Sakowicz, 2021). No linear peptides, but several natural AMPs have made it to the market. The peptide antibiotics bacitracin, polymyxin, gramicidin, and tyrothricin were among the first to be used in medicine (Sumi et al., 2015). *Bacillus* is an example of the bacteria that produce other peptide antibiotics. Tyothricin,the first AMP to be utilized in a clinical setting is composed of two major ingredients namely: tyrocidine and gramicidin. Because of its hemolytic effects, tyrocidine is a combination of cyclic decapeptides that is only used topically (Stevenson, 2009). Also, due to their hemolytic adverse effects, the broad-spectrum cyclodecapeptides tyrocidine A and gramicidin S can only be applied topically (Mösges et al., 2011, Murugaiyan et al., 2022).

The cyclic lipopeptides polymyxin B and polymyxin E (also called colistin) have been used to treat Gram-negative infections, and they are presently the last-resort treatment for MDR Gram-negative infections (Rabanal and Cajal, 2017). Due to their nephro- and neurotoxicity, polymyxins have a limited application; however, by using a prodrug formulation, their acute toxicity is mitigated by the matching sulfomethylated molecule. Nisin, a different naturally occurring (34-residue) AMP derived from *Lactococcus lactis*, is efficient against Gram-positive bacteria, particularly the pathogens that cause mastitis. Owing to its low toxicity, some countries such as England, Ireland and Denmark have granted the use of nisin as preservative in food industry to prevent proliferation of foodborne pathogens (Deegan et al., 2006). The treatment of infections brought on by MDR Gram-positive organisms includes the use of daptomycin, another cyclic lipopeptide (Humphries et al., 2013).

AMPs are highly effective against vegetative cells. For instance, the EmPis-1L peptide effectively destroys the antibiotic-resistant VBNC state cells of foodborne pathogenic bacteria like *Escherichia coli* O157 and *Vibrio parahaemolyticus* OS4 (Hu et al., 2019). Additionally, AMPs are capable of destroying bacterial biofilms structures (Yasir et al., 2018). AMPs LL-37 and α-defensin, salmine, lactoferrin, protamine, casecidin and isracidin, fibrinogen, pleurocidin, ll-AMP1 peptide, α-poly-l-lysine (poly-lys), α-poly-l-arginine (poly-arg) are notable examples of eukaryotic AMPs with therapeutic potential against foodborne pathogens (Wu et al., 2013, Cheng et al., 2015, Wu et al., 2016).

In order to overcome the issue of toxicity in the use of AMPs in clinical practice (human and veterinary sectors), diverse forms of approaches to enhance AMP stability are being considered. These include synthesis of constrained, hybridized, mimetic, immobilized and conjugated AMPs (Vallabani and Singh, 2018, Mitra et al., 2021). Among them, the conjugation of AMPs with conventional antibiotics is showing promise due to the possible synergistic interaction between the two drugs, which enables effective targeting and death of a number of pathogenic-resistant bacteria (Grassi et al., 2017, Li et al., 2018). For instance, when used to treat vancomycin-resistant Enterococci, AMP magainin and vancomycin exhibited very promising outcomes (Arnusch et al., 2012). By combining the cationic AMP ubiquicidin with chloramphenicol via a glutaraldehyde linker, similar outcomes were obtained, demonstrating increased antibiotic activity against *E. coli* and *Staphylococcus aureus* and decreased toxicity against human cells (Reinhardt and Neundorf, 2016). It's interesting to note that promising outcomes have also been obtained by combining AMPs with antibiotics in an effort to improve *in situ* drug delivery, increase medication selectivity, and decrease toxicity (Riber et al., 2015). This depends on the fundamental mechanism of action of AMPs on the components of bacterial outer walls. Since they cannot enter the microbial cell when the antibiotic's resistance mechanism involves membrane alteration, AMPs work better in synergy with antibiotics than when used alone. By being able to get beyond this obstacle, AMPs might be able to revive antibiotic activity that has been lost (Sierra et al., 2017).

Recently developed nanocarriers—drug delivery systems based on nanotechnology—could develop into a potent tactic for the effective delivery of AMPs. By shielding peptides from extracellular breakdown by proteases and other peptide-hydrolyzing conditions, AMP administration via nanocarriers may be favorable. Targeted nanocarriers may also help with enhanced medication pharmacokinetic characteristics and target selectivity. Drug delivery

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mechanisms come in a variety of forms, including liposomes, micelles, polymeric nanoparticles, and dendrimers (Biswaro et al., 2018, Ritsema et al., 2018).

Bacteriophages

Bacteriophages (phages) are perhaps among the oldest and most prevalent biological entities that can infect and replicate within bacteria. As a result, they are crucial to maintaining the balance of an environment where bacteria are present (Jaglan et al., 2022). There is now curiosity in utilizing phage as a biocontrol weapon because of the numerous alluring properties these natural antibacterial agents possess (Sillankorva et al., 2012). These include, low toxicity to humans, selectivity by acting only on their host without harming the natural microflora, relatively easy to propagate, cost-effective and sustainable solution to the control of pathogens (Shousha et al., 2015, Korf et al., 2019, Montso et al., 2019). In addition to being absorbed, they have also been separated from various human body parts, demonstrating their close ties to humans (Petsong et al., 2019, Fiscarelli et al., 2021). In the days before antibiotics, phages were utilized to combat infectious diseases agents soon after their discovery. However, their usage for therapeutic purposes was discontinued in the Western world after the development of antibiotics. The lack of additional therapeutic options and the ineffectiveness of traditional antibiotics in treating and managing harmful bacterial strains have recently accelerated the revival of phage therapy (Jaglan et al., 2022). In previous study, Montso et al. (2021) demonstrated that lytic phages effectively reduced *E. coli* O177 cells under artificial rumen fermentation conditions, and could therefore be used as a biocontrol strategy in live cattle to reduce meat and milk contamination in slaughterhouses and milking parlors, respectively.

Mechanism of Action of Bacteriophages

Once they have injected their DNA, phages employ the machinery of the host to replicate and interpret the information needed to generate viral progeny (in the case of lytic phages) and enzymes like spannin, holin, and endolysin (Briers, 2019, Gondil et al., 2020, Abeysekera et al., 2022). Caudoviricetes utilise holin-endolysin or pinholin single arrest release (SAR) mechanisms to break the peptidoglycan link of the cell wall in Gram-negative hosts. This causes host lysis and the release of viral offspring during the lytic cycle (Abdelrahman et al., 2021). Conversely, in lysogenic or temperate phages, the viral genome fuses with the host genome to form a prophage and replicates alongside it over a long period of time (Nanda et al., 2015, Pinto et al., 2020). Prophage induction, or its excision from the genome, can happen in response to cellular internal or external stimuli such as antibiotics, heat, low nutrient condition and ultraviolet (UV) light (Nanda et al., 2015). As a result, vulnerable bacteria are lysed and offspring phages are released, which may then go on to lyse or lysogenize further susceptible bacteria.

Application of Bacteriophages as Bio-control Agents

Phages have been adopted in a variety of sectors including medicine and agriculture. Phages have been employed to eliminate spoilage organisms in a variety of foods (Table 2) in both clinical and laboratory settings, reducing food loss and the costs that come with it. Bacteria can contaminate food ingredients before, during, or after manufacture. Any of these stages can be stopped or reduced by using certain phages. As a result, phages have lately proven to have a wide range of applications for improving safety in a number of food products (Table 2).

Phage therapy has been successfully used in clinical settings to treat severe or persistent bacterial infections (Abedon, 2019). Phage therapy for the treatment of persistent infections has primarily been used in Georgia, Poland, and Russia (Nikolich and Filippov, 2020, Barron, 2022). The type of infection, the type of phage or phage-based products, the dose of phage, and the method of delivery all affect how well the therapy works. It was reported that the Shanghai Institute of Phages in China administered clinical phage therapy to patients with MDR illnesses (Wu et al., 2021).

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Table 2. Bacteriophages as bio-control agents against food-borne (food products and food contact surface) pathogens.

Phages	Sample	Technique	Outcome	Reference
BEC8 cocktail (38, 39, 41, CEV2, AR1, 42, ECA1, and ECB7)	Spinach leaves and romaine lettuce	Following a one-hour drying period in a biosafety enclosure, the leaves were spot-inoculated with bacteria. On top of the previously inoculated leaf, BEC8, Trans-cinnamaldehyde, or TSB was administered. Without dehydrating the bacterial inoculum, positive controls were generated by combining it with BEC8 or TC.	Cell counts were reduced by both BEC8 and Trans-cinnamaldehyde at the various MOIs and temperatures. The effect of the BEC8 cocktail on both liquid and desiccated cells was identical. An augmentation of the antimicrobial effect was observed upon the combination of both agents.	Viazis and Diez-Gonzalez, 2011
A cocktail composed by the phages e11/2 and e4/1c	Cattle hide	The phage cocktail was introduced into the organism using a portable spray container. Negative control: An absence of wash treatment was observed.	After one hour of application to the cattle hide, phage cocktail demonstrated enhanced efficacy. The degree of bacterial eradication was equivalent to that obtained by washing the sample with water alone, when the sampling was conducted immediately following phage application	Coffey et al., 2011
BEC8 cocktail	Sterilized hard surfaces (stainless steel chips, ceramic tile chips, and high density polyethylene chips - HDPEC).	The semiconductor was spot-treated with bacteria before being dried in a biosafety cabinet. Prior to inoculation, the chip surface was treated with BEC8 or TSB. MOIs of 1, 10, and 100 were utilised. To generate positive controls, the bacterial inoculum was combined with BEC8 or TC without the process of dehydrating	Phage cocktail exhibited superior performance rating in inactivating the bacterial mixture across a range of conditions, including low to high MOIs, low to high temperatures, and shorter to extended periods of exposure. Both under arid and liquid conditions, bacterial levels could be regulated by phages. Phage-insensitive variants were not identified	Viazis et al., 2011 Tomat et al., 2018
Cocktail compose by phages DT1 to DT6	Milk and meat	Sterile, commercially available milk that had been reconstituted with $CaCl_2$ was used to inoculate one bacterial strain per batch. One portion of each batch was subjected to a phage cocktail, while the other was set aside as a control. 0.4 cm thick, 1 cm^2 portions of meat were spot-treated with bacterial strains and	Phage cocktail could detectably reduce the quantity of various *E. coli* isolates tested at 4 °C. A decrease in value was observed at higher temperatures (25 and 37 °C), but it persisted only during the initial hours of incubation. Phage cocktails	Hudson et al., 2016

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FAHEc1	UHT milk; Ready-to-eat meat; Raw beef	left to adhere for 10 minutes at room temperature. Following this, a phage cocktail was introduced into every meat piece. In order to establish controls, TMG buffer was added.	induce greater *E. coli* reduction in meat at elevated temperatures.	Le et al., 2018
phiEco1, phiEco2, phiEco3, phiEco5, phiEco6 and phiS1	Oyster	Before being applied to food products, phage FAHEc1 was exposed to ultraviolet radiation; phages are capable of lysing bacterial cells, even if they lose viability. Phages and *E. coli* O157:H7 were utilised to inoculate UHT milk.	A decline in cell count was observed exclusively with an increased phage concentration, encompassing both UV-treated and untreated phages. Untreated phages generally produce superior outcomes in milk. Consistency in observations was maintained for the control in RTE meat. The utilisation of UV-treated phages resulted in a more pronounced reduction of the host in uncooked beef	Ramirez et al., 2018
Phages phiJLA23, phiKP26, phiC119 and phiE142	Tomatoes	Inoculating raw beef at 37 °C simulated phage application immediately prior to slathering in carcasses	Attenuating all bacterial genotypes is possible with a high concentration of phages. When bacteria are present singly or in combination, a reduction is observed	
		At 37 °C, bacteria that had been grown overnight were introduced to the oysters and allowed to adhere for one hour. After adding phage suspension, the oyster meat was incubated at 3 °C for two days, followed by two hours at 37 °C		Akmal et al., 2020
			The concentrations of *E. coli* O157:H7 in tomatoes encapsulated with microencapsulated phages were substantially reduced after 24 hours at 4 °C, in comparison to the control group that did not receive the phage cocktail. The observed differences persisted for a duration of five days. Free phages are less stable in the presence of stress factors than microencapsulated phages.	Li et al., 2016
AKH-2	*Misgurnus anguillicaudatus*	A mixture of phages comprising 10^9 PFU/mL of each phage. In addition, microencapsulated phages were generated by combining a polymer mixture comprising 30% phage cocktail, 60% SM Buffer, and 10% solids (modified starch and maltodextrin). The tomato plants were categorised into three groups: the first group received *E. coli* O157:H7 inoculation, the second group		
PVS-1, and PVS-2, PVS-3	*Apostichopus japonicas* (Sea cucumber)			Luo et al., 2018
HN48	*Oreochromis niloticus* (Nile tilapia)			

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	received a microencapsulated cocktail phage inoculated with the bacterial host, and the third group served as a control without any inoculation	Phage-treated loach exhibited a higher survival rate In contrast to the single phage and control groups, the phage cocktail-treated group exhibited an 82% survival rate
	Loach immersed against *Aeromonas hydrophilia*	60% greater survival rate than the control group
	Individual phage or cocktail supplementation of the diet to combat *Vibrio splendidus*	
	Containment of *Streptococcus agalactiae* by means of phage preparation introduced to the tank	

Application of Bacteriophages as Bio-sensor

Beyond the therapeutic application of phages, genetically engineered phages can be utilized to identify individual bacteria even in a combination of many different bacterial species; bio-sensors. Typically, sensors have two or more useful parts. The first step is some sort of target recognition aspect. Second, there must be some sort of reporting transducing mechanism for when the recognition element finds that target. Phages function something like sensors (or, more exactly, a biosensor). The target, a host bacteria, is located by the proteins that bind to receptors. The reporter is the phage's genome, which produces other phages once it enters the target cell and may take the form of a plaque. Phages are extremely particular in identifying their target in this way, which can be a significant advantage in a biosensor (Gibb et al., 2021). Several methods use the typical phage recognition components to identify bacteria while modifying the reporter to increase the sensitivity or speed of the detection. Many detection methods merely depend on phage reproduction to signal the presence of the matching host cells (Ahovan et al., 2020, Meile et al., 2020).

Regulations for the Application of Phage Therapy

Phage therapy utilization in treatment regimens is not governed by any particular, global standards. Different standards for employing phage treatment in clinical cases have been developed by regulatory agencies around the world. Patients are treated in the United States under the FDA's emergency investigational new drug (eIND) approval, whereas Australia has created a specific access program and Belgium is using a magistral phage method (Donovan, 2017, Jarow et al., 2017, Pirnay et al., 2018, Djebara et al., 2019). The widespread use of phage therapy has been hampered by the inconsistent restrictions in different nations. However, the first phage therapy facility in the United States, UC San Diego Center for Innovative Phage Application and Therapeutics, has just been founded, and numerous patients have successfully undergone phage therapy with no negative effects reported (Aslam et al., 2020).

A phage-based anti-*E. coli* O157:H7 product called EcoShield™ was developed for use in red meat (Retrieved from the Intralytix website at http://www.intralytix.com/index.php?page=prod&id=2, October 2022). A different product called "Secure Shield E1" from the German company FINK TEC GmbH is intended to be used on the surfaces of beef carcasses. Each product has received FDA approval. Recent approval for the use of phage mixtures from OmniLytics (Sandy, UT), Micreos' PhageGuard E., and Intralytix's EcoShield PX™ to prevent shiga toxin producing *E. coli* (STEC) infection on a variety of food products was granted (Retrieved from https://www.fda.gov/food/generally-recognized-safegras/gras-notice-

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inventory, October 2022). The FDA approved the aforementioned phage products as generally recognized as safe (GRAS) food additives.

Other countries have also approved the use of phage to guarantee food safety. The National Food Service of the Israeli Ministry of Health approved all phages that had already been approved by the FDA to be used for analogous purposes in 2014 under the regulations titled "Guidelines: use of bacteriophages (bacteria-killing viruses) in food (Brüssow, 2019)." In Canada, phage-based products such as PhageGuard L™ (formerly Listex™), ListShield™, SalmoFresh™, and EcoShield™ have been authorized as aids in food processing (Brüssow, 2019). For some ready-to-eat (RTE) products, the Food Standards Australia New Zealand in Australia and New Zealand approved the use of phage-based treatments to control *Salmonella* and *Listeria monocytogenes* as processing aids. In Europe, the situation is somewhat different. Despite previous attempts to approve phage-based products, none of them have yet to display the "CE mark". Despite the regulatory barriers, Listex™ P100 has petitioned for clearance to be used as a decontamination agent to lower the level of *L. monocytogenes* in food, raw seafood (EFSA, 2012), and RTE food items (EFSA, 2016). To stop *Listeria* from developing in many food products, several food companies are already employing this phage product. In the absence of a regulatory framework from the European Union (EU), the European Court of Justice announced a court order in October 2019 permitting food producers to continue using phages to prevent *Listeria* on all RTE meals. European, American, Japanese, and other regulatory organizations acquired unified standards for the development of pharmaceuticals through the International Conference on Harmonization (ICH) (Jaglan et al., 2022).

Nanotechnology

Nanotechnology-based methodologies are employed across a range of disciplines, including engineering, material sciences, biology, and medicine. Nanomaterials are often defined as substances having sizes between 1 and 100 nm. To help provide distinctive features for a wide range of functions, they come in a variety of forms and sizes. When restricted to a relatively small scale, the material's characteristics experience considerable modifications. Nanomaterials are typically made of metals, metal oxides, or composites made of carbon and emulsions (Mubeen et al., 2021). A paradigm change in antibacterial medicine has been brought about by the use of nanoscale materials as antibacterial agents. High surface area to volume ratio nanomaterials are being researched for the creation of potent bactericidal medications because they can enhance interactions with the target agents. They demonstrate efficacy against bacteria that have already developed resistance through the use of mechanisms that are fundamentally different from the modes of action of conventional antibiotics. They also target a number of biomolecules, posing a threat to the emergence of resistant strains (Adhikari et al., 2022).

Nanomaterials have been found to have increased membrane permeability, the capacity to function as efflux pump inhibitors, and the potential for a variety of antibacterial actions, making them less likely to produce bacterial resistance than conventional antibiotics (Rudramurthy et al., 2016, Slavin et al., 2017). In addition to providing important pharmacological advantages such as improved drug solubility and half-life, extended and stimuli-responsive drug release, site-targeted administration, and combination treatment, nanoparticles (NPs) are valuable as antimicrobial vector (Colilla and Vallet-Regí, 2020, Spirescu et al., 2021).

Classification of Nanomaterials and their Properties

Numerous nanostructures, including liposomes, NPs, and dendrimers, have demonstrated their capacity to increase the effectiveness of antibiotic treatments and fight infectious diseases (Lee et al., 2019, Singh et al., 2019). Nanomaterials have been investigated in vitro and in vivo to control and combat bacterial infection, including antibacterial polypeptides, noble metal NPs, nanocomposites, semiconductor NPs, polymeric nanostructures, and carbon-based nanomaterials (CNMs) (Yeon et al., 2019, Mba and Nweze, 2021, Mubeen et al., 2021). We have also discussed extensively on the various forms of synthesis, characterization, probable mode of action, application and/or antibacterial

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activities and advantages of nanotechnology over antibiotics in our previous works (Ajose et al., 2022b, Abolarinwa et al., 2022)

Since severe membrane damage would require extensive regeneration of membrane components, which would be physically taxing for target cells, membrane-acting NPs are anticipated to be highly alluring and detrimental to the establishment of resistance. Modern physicochemical polymeric NPs have been proven to be a breakthrough treatment for bacterial diseases in humans (Spirescu et al., 2021). In comparison to currently available substances, this family of nanocarriers have a number of benefits including being proven to be safe, biodegradable, biocompatible, swiftly eliminated, and non-toxic to tissues and organs with superior pharmacokinetics properties. Additionally, this kind of therapy represents a breakthrough due to its ability to target a particular organ, reduce the adverse effects of numerous antibiotics, and gradually accumulate in the area that is diseased thus, more effective than conventional antibiotics for a longer period of time, which is crucial for a long-lasting, sustained therapeutic impact. The antibacterial potential of many inorganic (metal) NPs, including gold (Au), silver (Ag), and others, has been demonstrated (Gharpure et al., 2020, Sánchez-López et al., 2020). With good thermal stability, low toxicity, and antibacterial qualities, Ag is a noble metal. It has been shown that polyurethane and plastic catheters with AgNP surface functionalization are effective at preventing the growth of biofilms on a variety of harmful bacteria (Prasher et al., 2018).

Due to their distinctive physicochemical characteristics, CNMs have garnered general acceptance in the scientific community, but their clinical efficacy has not yet been established. These materials' insoluble nature, which makes it difficult for them to enter biological systems, is overcome by carbon nanostructures with programmable morphologies. Due to their capacity to eliminate harmful bacteria and stop their adhesion and biofilm formation, carbon NPs in general are promising antibacterial candidates with a range of biological applications (Xin et al., 2019, Azizi-Lalabadi et al., 2020). In bacteria, the adsorption of positive ions such as Ag^{+}, Cu^{2+}, and Zn^{2+} onto the bacterial cell membrane can lead to the breakdown of the cell wall and the creation of pits (Gupta et al., 2019a). A breakthrough in this kind of therapy is also represented by the targeting of a particular organ, the reduction of many antibiotics' side effects, and the sustained accumulation in the infected area over time. Au, Ag, and other inorganic NPs have demonstrated antibacterial properties (Gharpure et al., 2020, Sánchez-López et al., 2020). A noble metal with good thermal stability, low toxicity, and antibacterial qualities is Ag. AgNP surface functionalization of polyurethane and plastic catheters was shown to be effective at preventing the growth of biofilms from a variety of pathogenic bacteria (Prasher et al., 2018).

Applications of Nanotechnology

Although NPs are among the most effective weapons against MDR bacteria, the pharmaceutical industry still faces challenges in translating NP-based therapies into everyday use because nanotechnology hasn't yet permeated clinical practice. However, Martinez et al. (2020) demonstrated the capacity of photoactive metallated porphyrin-doped conjugated polymer NPs to eliminate pathogenic bacterial strains, such as antibiotic-resistant bacteria of the *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. (ESKAPE) pathogens group. Methicillin-resistant *S. aureus* (MRSA) can cause major infections with high morbidity and death in both the community and the hospital because it has evolved resistance to nearly all antibiotics. Functional nanomaterials and NPs can kill MRSA and be used in anti-MRSA therapy (Gao et al., 2021).

Some NPs are in clinical trials or have already received FDA approval for use in humans, and numerous proof-of-concept studies using nanomaterials in cell culture and small animal models are now underway (Anselmo and Mitragotri, 2016, Ventola, 2017). According to Gupta et al. (2019b), the biofilms of *S. aureus* and *P. aeruginosa* isolated from food were found to be susceptible to a concentration of 62.5 mg/mL of AgNP, but doses of 125 and 250 mg/mL of the same NP inhibited biofilms by 85 and 90%, respectively. In a another study, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of green synthesized AgNPs against MDR *P.*

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aeruginosa (MDR-PA) were reported as 3.88 ± 0.13 and 7.77 ± 0.25 g/mL and 7.77 ± 0.25 and 31.08 ± 1.01 g/mL against MRSA, respectively (Ansari et al., 2021).

Ethno-medicine

The Effect of Antibiotic Resistance on Sustainable Development Goals

The best plan currently available for creating a better world for people and the planet by the year 2030 is the set of 17 United Nations Sustainable Development Goals (UN SDGs). The UN SDGs, which were adopted by all United Nations Member States in 2015, are a call to action for all nations; rich, middle-income, and poor, to advance prosperity while preserving the environment. The fight against AMR and the SDGs go hand in hand. AMR has an impact on achieving a number of the 17 SDGs, especially SDG 3: "Good health and well-being."

AMR is now officially mentioned under SDG 3, and fulfilling many SDGs also depends on properly addressing AMR. First, with the use of efficient antibiotics, epidemics of infectious diseases including human immunodeficiency virus (HIV), gonorrhea, and tuberculosis can be controlled as well as maternal, neonatal, and pediatric fatalities can be avoided (SDG 3). Second, antibiotics are crucial for human health as well as the production of food and animals as well as for livelihoods (SDG 8, 2, 1). Third, improperly handled medical waste and wastewater can introduce antibiotic-resistant bacteria into soils, drinking water, and groundwater (SDG 6, 12). Finally, collaboration is necessary to combat AMR. The Tripartite, a group made up of the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE), has chosen to address AMR using the One Health strategy (SDG 17) (CDC, 2022, WHO, 2022).

The recently introduced SDG indicator on AMR intends to lower the percentage of bloodstream infections brought on by *E. coli* and *S. aureus* that are resistant to 3rd-generation cephalosporin drugs and methicillin, respectively. The ability to treat infections with currently available antibiotic will ultimately be preserved by the effective management of these two categories of antibiotic resistant pathogens while new preventative and treatment approaches are developed (WHO, 2022).

Plants Secondary Metabolites: Key Drivers of Pharmacological Actions of Medicinal Plants

Natural and/or organic by-products continue to be crucial to the success of drug development. Therefore, biological variety provides a never-ending supply of novel chemical entities (NCEs) with the potential to be therapeutic leads. These NCEs are made from substances that plants produce to protect them from herbivores and diseases or to entice pollinators. The vast majority of chemical compounds that are produced by plants, known as secondary metabolites, are those that are indirectly linked with development and growth (Harborne, 1999). Indicators of the potency of natural items as modern medications include the effectiveness of secondary metabolites in plants (Jahn et al., 2012). The biological effects of secondary metabolites have been shown to vary, providing the scientific underpinning for the use of herbs in traditional medicine in many ancient communities. They are able to shield plants from pathogens because they are antibiotic, antifungal, and antiviral in nature. They also have antibiofilm or anti-quorum sensing function (Adhikari et al., 2022). According to their chemical structures, plant secondary metabolites are divided into a variety of classes which include: phenolics (tannins, coumarins, flavonoids), alkaloids (ergots, imidazoles, pyridines, purines, quinolines), saponins (steroidal or triterpenoidal saponins), terpenes (mono-, sesqui-, sester-, hemi-, di-terpenes), lipids (fixed oil, waxes, essential oil) and carbohydrates (mono-,di-,oligo- and polysaccharides) (Bennetts et al., 1946).

Ethno-medicine as an alternative to antibiotic

Since the dawn of time, people have had close relationships with plants for use as food, fuel, medicine, and clothing. The use of medicinal plants is common in both industrialized and developing nations, and it has a long history even before antibiotics were produced (Alli and Mangamoori, 2016, Anju et al., 2022). Currently, as a result of the development and the effects of resistance to antibiotics, millions of people in developing nations throughout the world use medicinal plants and other natural

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goods as a way to treat infectious diseases. The market for the use of natural products for therapeutic purposes is expanding at a rapid rate. Ethno-medicine is applied in various sectors of life including medicinal, pharmaceutical and agricultural. Plants are sleeping giants of the modern pharmaceuticals. Hence, they are being explored as alternative antimicrobials. Several researchers have reported the activities of medicinal plants in the various sectors (Ajose and Okozi, 2017, McGaw et al., 2020, Mwinga et al., 2022, Ajose et al., 2022a), usage and antimicrobial form of secondary metabolites (Table 3).

Globally, the plant kingdom offers a variety of species that are used as therapies for different illnesses (Brusotti et al., 2014). According to World Health Organization (WHO) reports, a significant portion of the global population uses traditional medicines, including those that use plant decoctions or functional chemicals (WHO, 1991, WHO, 2013). The most crucial need for using an ethno-pharmacological approach is knowledge of the plant parts previously employed as remedies. The two most well-known traditional therapies for treating various illnesses are Chinese herbal medicine and Ayurveda, but in areas where there are no texts to consult, ethno-botanical surveys are the only method to learn about the traditional use of medicinal plants.

Table 3. An overview of medicinal plants secondary metabolites.

Secondary metabolite (SM)	Characteristics	Sub-category of SM	Uses	References
Phenols	Probably constitute the largest group of plant SMs, They share the presence of one or more phenol groups as a common feature and range from simple structures with one aromatic ring to highly complex polymeric substances Widespread in plants and contribute significantly to the color, taste and flavor of many herbs, foods and drinks	Quercetin	Anti-inflammatory	(Goławska et al., 2014, Hussein and El-Anssary, 2019)
		Flavonoids	Antioxidant, anti-inflammatory and anti-allergic effects, anti-tumor	(Montanher et al., 2007, Serafin et al., 2009)
		Gallic acid, Phenol	Antibacterial, antiviral, antifungal, anti-inflammatory, antitumor, anti-anaphylactic, antiseptic, anti-mutagenic, choleretic and bronchodilatory actions	(Pelczar et al., 1988, Yarnell, 2002, Spiller et al., 2008)
		Tannin	Anti-diarrhea, antidote, antiseptic	(Jepson et al., 2013)
		Coumarin	Anti-inflammatory, anticoagulant, anticancer and anti-Alzheimer's	(Xu et al., 2015)
Alkaloids	Organic compounds with at least one nitrogen atom in a heterocyclic ring. Except for the fact that they are all nitrogen-containing compounds,	Aromatics, Carbolines, Ergots, Imidazoles, Pyridines, Purines, Quinolines, Piperidines, etc.	Analgesia, local anesthesia, cardiac stimulation, respiratory stimulation and relaxation, vasoconstriction muscle relaxation and toxicity, as well as antineoplastic, hypertensive and hypotensive properties.	(Seigler, 1998, Hoffmann, 2003, Hussein and El-Anssary, 2019)

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	no general definition fits all alkaloids. Many are toxic to animals to cause death if eaten		antibacterial, antifungal, antiviral	
Saponins	This hydrophobic-hydrophilic asymmetry means that these compounds have the ability to lower surface tension and are soap-like. They form foam in aqueous solutions and cause hemolysis of blood erythrocytes in vitro.	Pentoses, Hexoses, or Uronic acids	Antitumor, piscicidal, molluscicidal, spermicidal, sedative, expectorant, anti-inflammatory and analgesic properties.	Rehab 2018 (Hussein and El-Anssary, 2019)
Terpenes	Most diverse group of plant SMs All forms are derived chemically from 5-carbon isoprene units assembled in different ways Classified according to the number of isoprene units in the molecule	Monoterpenes, Sesquiterpenes, Sesterterpenes, Hemiterpenes, Diterpenes Triterpenes	Anti-hemorrhagic, analgesic, antibacterial, antifungal, anti-inflammatory, antineoplastic and antiprotozoal activities, anti-rheumatics	(Hoffmann, 2003, Culioli et al., 2003)
Lipids	Major structural components of all biological membranes Source of energy reservoirs and fuel for cellular activities in addition to being vitamins and hormones Although lipids are primary metabolites, recent studies revealed pharmacological activities	Fixed oils, Waxes, Essential oils, Sterols, Fat-soluble vitamins (such as vitamins A, D, E and K), Phospholipids and others	Anti-inflammatory, anti-aging, wound healing activities, antiseptic, antimicrobial, analgesic, sedative, spasmolytic and locally anesthetic remedies. They are also used as fragrances in embalmment, as sunscreens, moisturizer and in food preservation	(Masotti et al., 2003, Fahy et al., 2009, Subramaniam et al., 2011)

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	to members of this class of SMs			
Carbohydrates	Starter for all SMs and animal biochemical. Although carbohydrates are primary metabolites, they are incorporated in plenty of SMs through glycosidation linkages. Polymers of simple sugars and uronic acids produce mucilage and gums	Monosaccharides, Disaccharides, Oligosaccharides and Polysaccharides	Demulcent, emollient	(Asif et al., 2011, Anbalahan, 2017)

Probiotics and Prebiotics

For today's health-conscious population, food serves as more than just a source of energy; they also look for food components and nutrients that can improve health benefits or avoid chronic diseases (Webb, 2011). The emphasis of nutritional biology is therefore on "functional foods," which largely consist of probiotics, prebiotics, and synbiotics. Additionally, functional foods give the body the necessary amounts of lipids, proteins, carbohydrates, and vitamins (Cencic and Chingwaru, 2010). Prebiotic and probiotic techniques involve the use of microbial food supplements that benefit the host by enhancing the balance of intestinal microbes. Prebiotics and probiotics are preferable to antibiotics for treatment since they are safe for long-term usage and do not induce allergies or negative effects (Ghosh et al., 2019).

Applications and Mechanism of Action of Probiotics

Dietary fibers known as prebiotics are frequently combined with probiotics to increase their viability. The most common prebiotics include fructo- and galacto-oligosaccharides (FOS and GOS), xylo- and oligosaccharides (XOS), inulin, and fructans. Synbiotics is a common word for the combination. Therefore, synbiotics are a carefully chosen combination of probiotics and prebiotics that aid in the development of a balanced microbiota in the intestine of the host. It is crucial to reach agreement on the makeup and functions of probiotics, prebiotics, and synbiotics in promoting human health. Some of the probiotics drugs marketed worldwide include enteral capsules (Vanhee et al., 2010), acidolac (Zawistowska-Rojek et al., 2016), biogermin (Celandroni et al., 2019), entromax (Kesavelu et al., 2020), bifilac GG (Kesavelu et al., 2020), and gutpro (Kesavelu et al., 2020). Probiotics have been found to have other immunomodulatory activities that are advantageous in conditions like allergies, cancer, obesity and type 2 diabetes, aging, fatigue, autism, osteoporosis, and others, in addition to limiting the growth of drug-resistant bacteria (Harish and Varghese, 2006).

Probiotic effects vary based on the strain combination employed (Prado et al., 2015). According to recent studies, using probiotics can help prevent or treat yeast infections that develop as a result of antibiotic use, abnormalities of the lower intestine's epithelium caused by *Clostridium difficile*, and antibiotic-associated diarrhea (AAD) in humans (Ferreira et al., 2017, Adhikari et al., 2022), as antimicrobial agents against foodborne pathogens (Li et al., 2014), reduction of cross-contamination and dissemination of infections (Crouzet et al., 2015), as feed additives in agricultural production (Frizzo et al., 2018, Mohamed et al., 2019, Ringø, 2020), and combating biofilm formation of pathogenic *E. coli* (Fang et al., 2018). de Melo Pereira et al. (2018) and (Tang et al., 2022) reported that several probiotic bacteria are known to produce a variety of antimicrobial substances, organic acids, and bacteriocins that can prevent the growth of bacteria that are resistant to multiple drugs.

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Forest ecosystem research revealed that fungal and bacterial communities can respond to environmental changes in accordance with their host trees (Park et al., 2020). Other research has shown that microbial and biochemical indicators of soil health can be used to evaluate the ecological risk of soil. These findings demonstrated that soil respiration can be utilized to estimate soil ecological conditions and microbial activity (Niemeyer et al., 2012).

In environmental health, probiotics play an essential role as agents of remediation, in assisting the host to adapt to environmental changes. Certain genera also function as bioremediation or decomposition agents of hazardous substances (Helmy et al., 2019), such as a bacterial consortium (Xanthomonadaceae, *Brachybacterium* sp., *Bhargavaea* sp., *Gordonia* sp., *Thalassospira* sp., *Pseudomonas* sp., *Dietzia* sp., *Mesorhizobium* sp., *Cytophaga* sp. Conventional remediation strategies for the majority of types of environmental contamination are not only costly but also ineffective, particularly at low concentrations of contaminants (Goyal et al., 2019). Probiotics-assisted remediation has emerged as an inexpensive and straightforward alternative.

The theory behind the use of probiotics is that once the microbial flora in the gut has returned to equilibrium, the commensal bacteria can outgrow and actively exclude harmful strains. These commensal bacteria foster disease resistance either directly, through interactions with other bacteria, or indirectly, by triggering host immune systems (Isolauri et al., 2002, Łojewska and Sakowicz, 2021). However, probiotics also carry the danger of introducing and/or transmitting AMR characteristics via a variety of routes and may also cause non-genetically determined resistance in the endogenous microflora (phenotypic susceptibility due to the probiotic strain) (Palma et al., 2020). To establish uniform procedures for evaluating the safety of probiotics before approving their use in clinical practice, several research groups and regulatory organizations are concentrating on resolving the issue of resistance (Ouwehand et al., 2016).

Established Probiotics Risk Assessment Protocol

Probiotics may be clinically effective, but it is still important to guarantee the safety of the involved microbe. It is preferable to talk about probiotic safety generally since it affects both people and farm animals. More significant than the source of the isolate are the specific properties of a probiotic. It is essential that a probiotic agent's potential endures for a long time at the site of action (Alayande et al., 2020). This implies that enough consideration must be given to the examination of a particular strain's risk factors. Due to their extensive history of usage as probiotics, the majority of probiotic strains have earned the designation "Generally Recognized as Safe" (GRAS) (Plessas et al., 2017). However, not all innovative probiotics may be expected to have the same safety record as the traditional strains. The synthesis of toxic biochemical, virulence factors, transferrable ARGs, and hemolytic potential are only a few of the unfavorable traits that probiotics may have (Lee et al., 2017, Ahmad et al., 2022). For instance, it has been underlined that there may be a risk of horizontal antibiotic-resistant gene (ARG) transfer from one probiotic strain to other bacteria in the host's gastrointestinal environment (Plessas et al., 2017). Along with this, there have also been a small number of reports of infectious disorders such endocarditis, bacteremia, pneumoniae, meningitis, and septic arthritis linked to specific *Lactobacillus* and *Enterococcus* strains, which have largely affected immunocompromised people (Vankerckhoven et al., 2008).

Although it is a member of the lactic acid bacteria, *Enterococcus* was listed as one of the bacteria with a high potential for virulence features in a joint study of the Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Consultation in Rome (FAO/WHO, 2006). Due to the fact that the *Enterococcus* genus frequently exhibits a high amount of vancomycin-resistant genes, its use as a probiotic has been discouraged.

Other potential risk factors that need to be highlighted include the potential to foster harmful metabolic effects, excessive immune stimulation, and toxigenicity of the particular strain, level of purity of the product, colonization and genetic stability of the strain over time (Suresh et al., 2013). Additionally, the FAO working group study (FAO/WHO, 2002) advises that prospective probiotic strains be examined for virulence in animal models with weakened immune systems and potential negative effects on end users. In addition, Kim et al. (2018) suggest the following guidelines for the

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safety assessment and regulation of probiotics, which have been approved by the European Union Scientific Committee on Animal Nutrition: taxonomical definition of the strains, collection of substantial information revealing data such as history of use, industrial applications, ecological niche, human intervention, exclusion of pathogenicity, and description of end users.

Conclusion and future perspective

Although the use of antibiotics in controlling bacterial infections is still necessary, it is critical to drastically reduce their use in all facets of One-Health by using alternate strategies to limit the pathogens. Since antibiotic resistance is mostly brought about by the abuse of antibiotics, antibiotic-free techniques are a viable new approach to deal with the current antibacterial dilemma. Hence, a range of approaches are required for both microbial illness prevention and treatment. The use of an effective combination of living and nonliving structures from natural resources is one of the promising "one health" approaches for addressing the disruption of human, animal, plant, and environmental health. From preclinical optimization to phase 3 studies, academic researchers and the pharmaceutical industries have successfully produced a diverse portfolio of potential antibiotic alternatives projects. Some approaches, such as nanomaterials, phage therapy, natural compounds, and probiotics, have been prioritized for more thorough review. These approaches have shown potential in studies, which are still in the early stages.

Further insight into how the alternative measures function to fight antibiotic resistant pathogens will come from a complete comprehension of the equilibrium between the opposing mechanisms of action and resistance. These discoveries may offer fresh approaches or models from which new drugs can be created to cure or prevent illnesses, particularly those brought on by microorganisms resistant to common antibiotics. In order to reduce pathogen resistance to host defenses, restore or amp up the actions of conventional antibiotics against drug-resistant infections and target strategic microbial structures or functions, pharmacologic compounds may be produced and identified. These viewpoints suggest that there may be numerous undiscovered or underappreciated mysteries about the alternative approaches mechanisms of action and resistance.

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