Chapter

Bacterial Biofilm: Contribution to AMR and Approaches to Tackle

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Abstract

The brisk emergence of resistant microbes is occurring worldwide, endangering the efficacy of various antimicrobial agents. The overprescription of antimicrobial drugs results in the emergence of mutant strains of drug-resistant pathogens challenging the existing antimicrobial regime. Moreover, the outbreak of the pandemic has emphasized the necessity to consider the coinfections and antimicrobial resistance crisis as a vital motive of morbidity and mortality. Therefore, the prevention of such infections is much better than the eradication of the same. Thus, herein, we aim at providing a comprehensive list that can be used as an alternative class of antibacterial agents by exploiting the activity of various phytochemicals. The antibiofilm activity of various classes of phytochemicals would be projected for both the eradication and the prevention of biofilm formation in the presence of selected compounds. This chapter visualizes antimicrobial resistance as a matter of grave concern and one of the greatest threats to global health, food security, and development today.

Keywords: biofilm, antimicrobial resistance, phytochemicals, antibacterial resistance

1. Introduction

Antimicrobials can be synthetic or natural molecules that have the efficacy to kill microorganisms effectively. The tolerance toward antimicrobials has emerged as a major challenge for scientists and doctors across healthcare sectors, and it is becoming a serious threat worldwide. Since the late 1960s, the situation is intensified by decline in the search of novel drugs, as testing new drugs and finally its acceptance requires long time periods by the authorities for commercialization [1]. Antimicrobial resistance (AMR) in pathogenic microbes is the threatening global health problem with the biggest threat to human health, and the world is suffering without any significant and effective antibiotics [2]. It occurs when bacteria, viruses, fungi, and parasites change over time and, now, no longer respond to antibiotics.

In other words, microbes become resistant to antibiotics and cause reinfection. Sometimes, it is impossible to treat such infection, and it ultimately increases the risk of disease spread, severe illness, and even becomes fatal day by day. According to recent studies and World Health Organization (WHO)'s reference, the antimicrobial resistant microbes are also referred to as "superbugs" sometimes. According to 2014 World Health Organization (WHO) report, "Antimicrobial Resistance: Global Report on Surveillance," the problem is "so serious that it threatens the achievements of

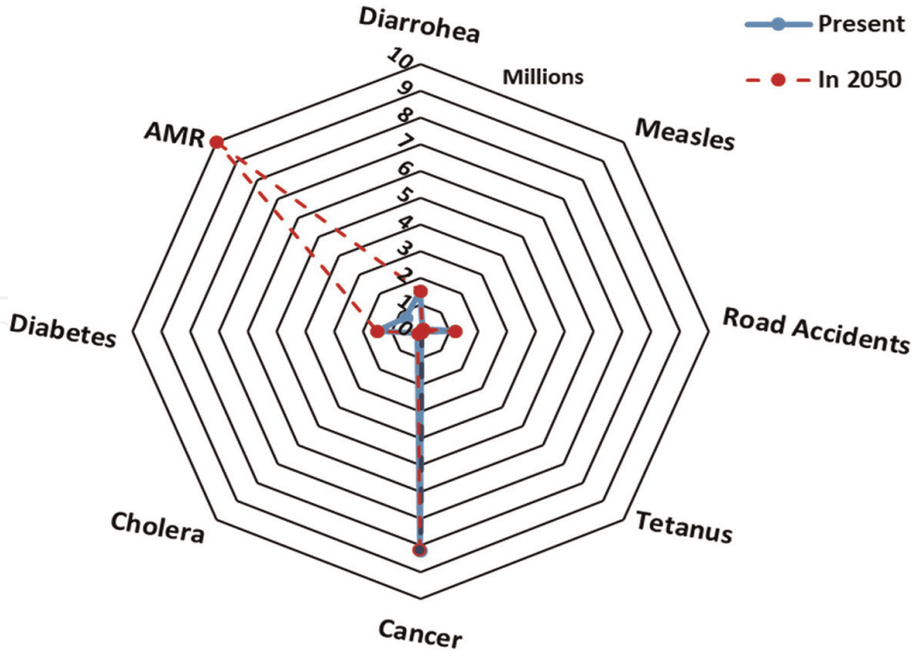


Figure 1.
The number of deaths per year (in millions) as per data provided by the report on the AMR review by Hala Audi in 2014.

modern medicine. A post-antibiotic era—in which common infections and minor injuries can kill—is a very real possibility for the 21st century" [3]. **Figure 1**, based on the report presented by Hala Audi in 2014 [3], shows the number of deaths (in million) versus various causes of death in the present age, and the number of deaths due to AMR is estimated to be increased from 700,000 at present to 10 million deaths per year in 2050 [4].

One of the major reasons contributing to the emergence of AMR is the overuse of antibiotics. At present, most of the antimicrobial compounds target the necessary microbial physiological processes, thereby exerting strong selection pressure on microbes that promote the emergence and spread of drug-resistant strains. Recently, researchers have targeted their research toward finding novel solutions to overcome AMR by targeting the cause of resistance. Phytochemicals, such as alkaloids, flavonoids, quinones, tannins, coumarins, terpenes, lectins, and saponins, have exerted potential antibacterial activities against sensitive as well as resistant pathogens [5, 6]. In this chapter, we have focused on AMR in bacteria, their mechanism of action specifically biofilm formation, and the probable ways to tackle them with emphasis on phytochemicals.

2. Antibacterial resistance

With the discovery of new antibiotics, resistance closely follows and develops continuously. The first antibiotic, penicillin (discovered in 1928), was soon followed by the identification of penicillinase, which led to the discovery of new β-lactams. Similarly, the discovery of sulfonamides, in 1937, led to the resistance in late 1930s. Therefore, each and every new discovery of antibiotics led to the emergence of resistance, leading to decreased treatment options and ultimately rise in morbidity

and mortality [7]. The antibacterial resistance is an ever-evolving genetic phenomenon that may be due to genetic mutations or horizontal gene transfer.

The multidrug resistance (MDR) in bacteria is increasing rapidly (**Table 1**), and in 2017, the WHO has categorized and prioritized the drug-resistant bacteria as "critical, high, and medium" for research of new antibiotics. The list includes carbapenem

Bacteria name	Resistant antibiotics	Illnesses caused	References
Gram-negative bacteria			
Acinetobacter baumannii	Carbapenem-resistant	Severe pneumonia, urinary tract infection (UTI), bloodstream infections.	[8, 9]
Pseudomonas aeruginosa	Fluoroquinolone-resistant	Generalized inflammation and sepsis pneumonia, septic shock, skin and soft tissue infections, UTI, gastrointestinal infections.	[10]
	β-Lactams resistance		
Enterobacteriaceae	Carbapenem-resistant	Multiple enteric problems	[11, 12]
	Third-generation cephalosporin-resistant		
Helicobacter pylori	Clarithromycin-resistant	Stomach inflammation and ulcers may lead to stomach cancer.	[13, 14]
Campylobacter	Fluoroquinolone-resistant	Diarrhea, dysentery	[15]
Salmonella spp.	Fluoroquinolone-resistant	Enteritis, osteomyelitis, meningitis, and osteitis.	[16, 17]
Neisseria gonorrhea	Fluoroquinolone-resistant	Gonorrhea	[18, 19]
	Third generation cephalosporin-resistant		
Haemophilus influenzae	Ampicillin-resistant	Pneumonia, bloodstream infection, meningitis, epiglottitis, cellulitis, and infectious arthritis	[20]
Shigella spp.	Fluoroquinolone-resistant	Dysentery	[21]
Klebsiella pneumoniae	Ceftazidime-avibactam	Pneumonia, urinary tract infections, bacteremia, and liver abscesses.	[22]
Gram-positive bacteria			
Enterococcus spp.	Vancomycin-resistant	UTI, bacterial endocarditis, diverticulitis, and meningitis.	[23–27]
	Ampicillin-penicillin and cephalosporin-resistant		
	Fluoroquinolone-resistant		
	Other resistance to aminoglycoside like tobramycin, kanamycin, and gentamicin		
Staphylococcus aureus	Methicillin-resistant	Pneumonia, meningitis, osteomyelitis, endocarditis, bacteremia, sepsis, toxic shock syndrome	[28, 29]
	Vancomycin intermediate and resistant		
	Other antibiotics resistance like linezolid and daptomycin		

Bacteria name	Resistant antibiotics	Illnesses caused	References
Clostridium difficile	Fluoroquinolone-resistant	Severe diarrhea and other intestinal diarrhea.	[30]
Clostridium perfringens	Streptomycin	Food poisoning (gastroenteritis) and clostridial myonecrosis.	[31, 32]
	Lincomycin		
	Trimethoprim-sulfamethoxazole		
Streptococcus pneumoniae	Penicillin non susceptible	Pneumonia, meningitis, bacteremia, otitis media, sinusitis	[33–35]
	Macrolide resistance		
	β-Lactams resistance		
	Fluoroquinolone-resistant		
	MDR pneumococcus		
	Resistance to other antibiotics like tetracycline and doxycycline		
Streptococcus spp.	Penicillin	Bacteremia, sepsis, pneumonia, and meningitis	[36–38]
	β-Lactams resistance		
	Macrolides		
	Fluoroquinolone-resistant		
	Streptogramins		
	Erythromycin		
Bacillus spp.	Penicillin resistance	Anthrax, food poisoning syndromes, septicemia, endocarditis, meningitis, and infections of wounds, the ears, eyes, RT, urinary tract, and gastrointestinal tract	[39]
	Ampicillin resistance		
	Cephalosporins resistance		
	Trimethoprim resistance		
Corynebacterium diphtheria	Chloramphenicol	Diphtheria and pharyngitis	[40–42]
	Sulfonamides		
	Tetracyclines resistance		
Listeria monocytogenes	Tetracyclines resistance	Listeriosis, diarrhea, muscle aches, etc.	[43]
	Fluoroquinolones resistance		

Table 1.
List of bacteria showing antibacterial resistance and the illness caused by them.

resistant (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, ESBL-producing) as critical priority; *Enterococcus faecium* (vancomycin-resistant), *Staphylococcus aureus* (methicillin-resistant and vancomycin-intermediate and resistant), *Helicobacter pylori* (clarithromycin-resistant), *Campylobacter* spp. (fluoroquinolone-resistant), *Salmonellae* (fluoroquinolone-resistant), and *Neisseria gonorrhoeae* (cephalosporin-resistant, fluoroquinolone-resistant) as high priority; and *Streptococcus pneumoniae* (penicillin nonsusceptible), *Haemophilus influenzae* (ampicillin-resistant), *Shigella* spp. (fluoroquinolone-resistant) as medium priority drug-resistant bacteria.

The antibiotics have a specific site of action in the bacterial cells, as shown in **Figure 2**. The antibiotic can cause defect in cell wall synthesis, inhibition of DNA

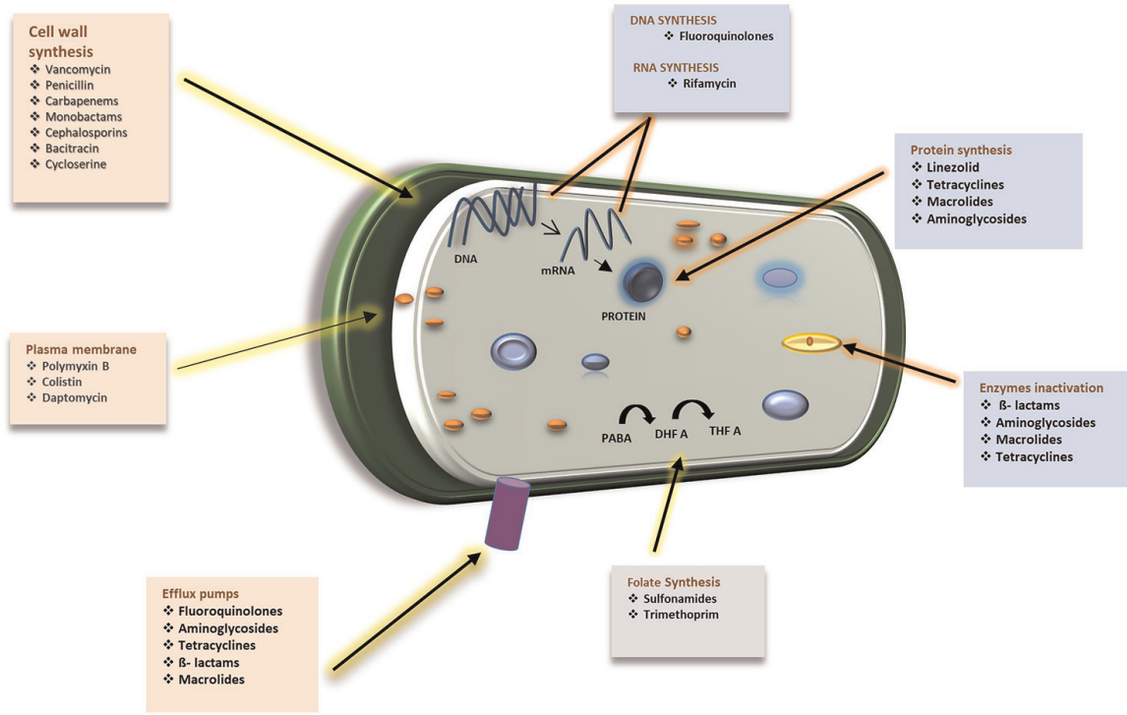


Figure 2.
Different classes of antibiotics and their site of action in the bacterial cell.

gyrase, topoisomerase IV, and translocation inhibition (via 30S ribosome subunit) leading to formation of nonfunctional proteins or protein synthesis inhibition (via 50S ribosome subunit) [44].

3. Mechanism of antibacterial resistance

Antibacterial resistance means that the bacterial cell is capable of escaping the effects of drugs by various mechanisms. These resistant mechanisms can be general like modification in structure, which results in the hindrance of drug attachment to bacterial cells, attainment of aminoglycoside modifying enzyme, neutralizing or pumping the antibodies outside by efflux pumps, mutation of DNA gyrase, decrease in the affinity to antibiotics, methylation and/or mutation of 23S rRNA, alteration of target sites like penicillin-binding proteins (PBPs), and inactivation of antibiotics. The specific mechanisms, such as the production of lactamases for the enzymatic degradation of lactam antibodies and affecting the susceptibility and affinity of the target sites as in gram-positive bacteria [45, 46], are also present. The mechanism can be either intrinsic or extrinsic resistance, which helps bacteria to acquire new resistant genes. Apart from these well-known genetic mechanisms, biofilm-formation- and quorum sensing (QS)-related responses are other important features that help bacteria to gain resistance. In this chapter, we will discuss about the role of biofilm and its formation in detail.

3.1 Biofilm

Biofilms are a complex three-dimensional densely packed architectural network of microbes residing inside the polymeric matter secreted by them on several biotic and abiotic surfaces. The biofilm concept was given in 1971 by Marshall et al. [47], and later,

Fletcher, Characklis, and Costerton described it as follows: "Biofilm is the unique pattern of growth in the life cycle of microbes that provides specific properties, advantages, and a higher level of organization to the free-living bacterial cells during colonization" [48]. According to the National Institutes of Health (NIH), 65% of microbial and 80% of chronic infections are linked to biofilm forming bacteria as compared to planktonic cells. The biofilm formation gives bacteria protection from antibiotics, disinfectants, and host defense system, thus showing resistance to them. For biofilm production, some bacteria adjust their gene expression and some use quorum-sensing systems. In both the gram-negative and gram-positive bacteria, quorum-sensing (QS) mechanisms exist, but the signal molecules used by them to transmit information are different. The QS signals of bacteria participate in various physiological processes such as motility, plasmid conjugation, biofilm formation, and antibiotic resistance to help them cope in the adverse environmental situations. The QS system comprises autoinducing peptides (AIPs), autoinducer-2 (AI-2), and acyl-homoserine lactones (AHLs) [49]. The presence of glycocalyx, outer membrane structure, efflux pumps, heterogeneity in growth rate, genetic adaptation, metabolic state, and metabolism of cells within a biofilm are the leading causes of biofilm that acquire resistance against antimicrobials [50]. As biofilms have extracellular polymeric substances (EPSs) that surround the cells, they provide protection to the microbial cells against harsh growth conditions [51]. EPSs are constituted of lipids, proteins, extracellular DNA, and polysaccharides. The biofilm formation is a multistep process, starting with attachment to the biotic or abiotic surface, forming a microcolony and then finally forming a three-dimensional structure, which, after maturation, starts the detachment of bacterial cells for another cycle of biofilm formation via attachment (**Figure 3**).

3.1.1 Attachment to the surfaces

The first initial step is the attachment step, which is further divided into a two-stage process: initial reversible attachment and irreversible attachment [52]. Biofilm

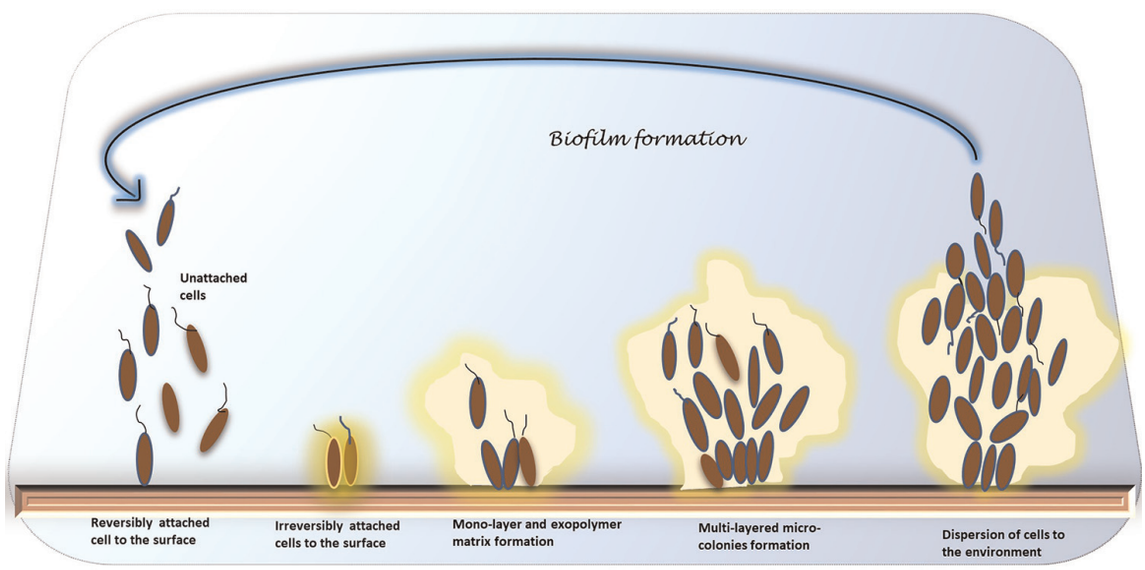


Figure 3.
Stages of biofilm formation: the formation begins with a reversible attachment of the planktonic cells (dark brown ovals) followed by the adhesion to the surface (light brown). The bacteria then form a monolayer and irreversibly attach by producing an extracellular matrix. Next, a microcolony is formed where multilayers appear. During later stages, the biofilm matures, and finally, some cells start to detach and the biofilm (shown in yellow) disperses, releasing planktonic cells for re-attachment.

formation begins by the preliminary reversible attachment of the planktonic microbial cells to the biotic or abiotic surface followed by adhesion. Bacteria will then start to form a monolayer and will produce an extracellular matrix (also known as slime) for protection. In this stage, the formation of microcolonies takes place, which shows significant growth and cell-cell communication for example quorum sensing. Now, the biofilm grows and the attachment is irreversible.

3.1.2 Maturation

This step initiates the cell growth that results in small colonies of microorganisms forming a characteristic "toadstool"-like structure. Bacteria within biofilm communities perform specialized functions after communicating via QS to each other. As the biofilm matures, more DNA, proteins, polysaccharides, etc., also known as biofilm scaffolds, are secreted by the bacteria residing within the biofilm. As the stage progresses, a heterogeneous physicochemical environment—mediated by van der Waals forces and hydrophobic and electrostatic interactions—is developed via the cell-to-cell interaction, which provides the embedded-cell-specialized physiological features. This environment inside the biofilm leads to specialized characters to the residing microbes for differentiation into the mature bacterial community for the final dispersion of the planktonic form [53].

3.1.3 Dispersion

After the biofilm maturation, some cells of mature biofilm start detaching and disperse into the environment as planktonic cells; this planktonic stage is considered as more sensitive to antimicrobials and immune responses. Therefore, dispersion is a very promising path for biofilm control. This mechanism is cyclic as the released microbial planktonic cells have the potential to again start a new biofilm formation cycle.

4. Approaches to tackle

The resistance of pathogenic microbes against the known drug is becoming a global problem. These pathogens also acquire resistance toward various drugs and, thus, termed as multidrug resistance (MDR). These MDR bacteria pose a major threat to community and health care as hospital-acquired secondary infections lead to longer stay in hospitals and complications. The common examples are *S. pneumoniae*, *E. faecium*, and *S. aureus*. Thus, active research for novel antibiotics or novel targets such as dodecyl deoxy glycosides, teixobactin, 2-((3-(3,6-dichloro-9H-carbazol-9-yl)-2-hydroxypropyl) amino)-2 (hydroxymethyl)propane1,3-diol (DCAP), and malacidins to combat such bacterial infections is the need of an hour. Moreover, natural compounds of either plant origin or microbial by-products as antimicrobials, such as cannabinoids, antimicrobial peptides, and odilorhabdins, are promising aspects of this research. The combinatorial strategy giving synergistic effect is also being used to tackle AMR such as probiotics and bacteriophages. Of these various strategies, this chapter will focus on plant products or phytochemicals that are being researched for their use to combat AMR by targeting various resistance mechanisms such as biofilm, quorum sensing, etc. (**Figure 4**).

Many present studies focus on the strategy for screening various phytochemicals, the method in the identification of their bioactive components, their further investigations, and various approaches that could be adopted to prevent the lethal

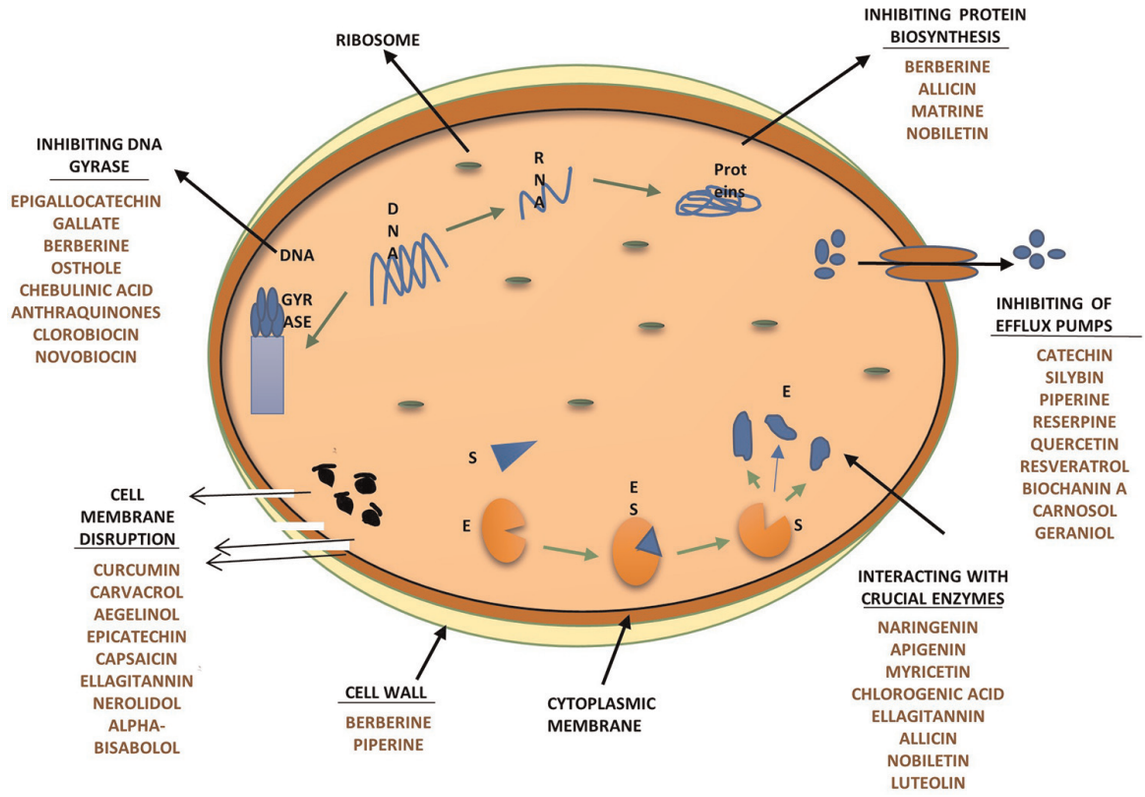


Figure 4.
Different types of phytochemicals and their site of action in the bacterial cell.

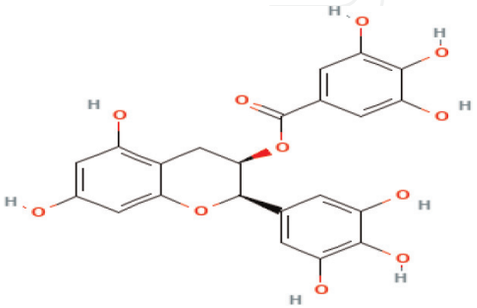
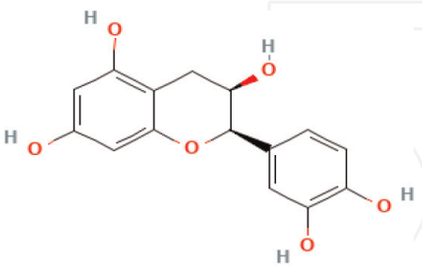
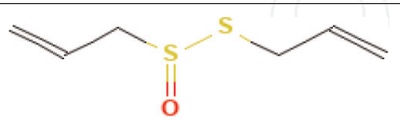
consequences of multidrug resistance. Phytochemicals have an immense potential to combat bacterial infections by disrupting the bacterial membrane, inhibition of cell wall or protein synthesis, interference with intermediary metabolism, damage to the synthesis and function of DNA/RNA, and normal cell communication interruption and induction of coagulated cytoplasmic constituents without any pronounced side effect. Major phytochemical classes studied are alkaloids, flavonoids, quinones, tannins, coumarins, terpenes, lectins, and saponins [5, 6]. **Table 2** depicts in detail the structure and common name of phytochemicals with their known mechanism of action.

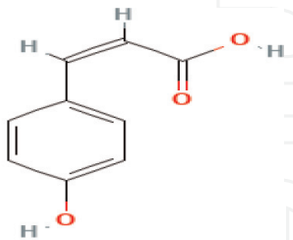
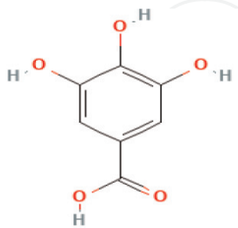
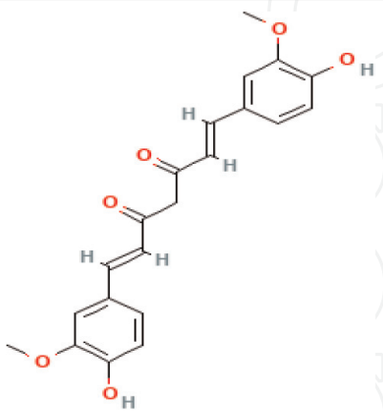
4.1 Phenolics and polyphenols

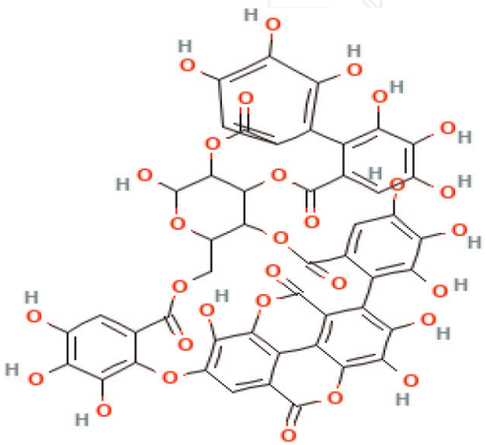
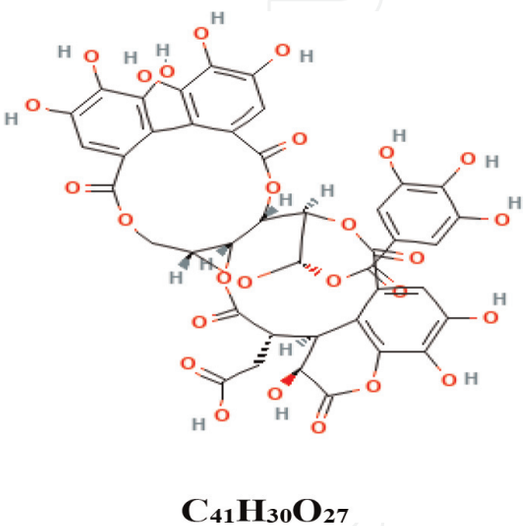
These is a diverse group of aromatic secondary metabolites consisting of flavonoids, quinones, tannins, and coumarins involved in plant defense mechanisms. They exhibit antibacterial properties against various bacteria. Among all flavonols, phenolic acids show maximum activities because they can interact with the cytoplasmic membrane, inhibit bacterial virulence factors including enzymes and toxins, suppress biofilm formation, reduce the pH values, reduce the extracellular polysaccharide activity, exert synergistic effects with conventional antibiotics, and finally can act as EP inhibitors [77].

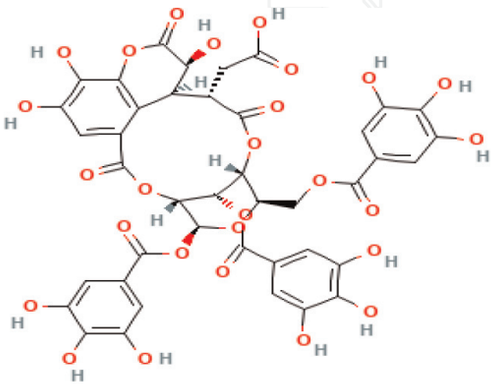
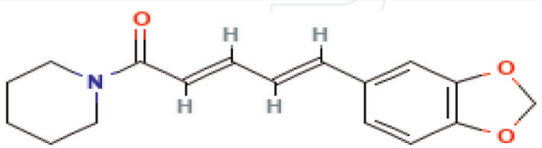
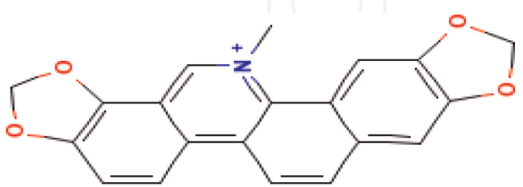
4.1.1 Flavonoids

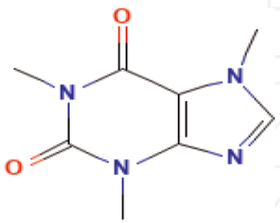
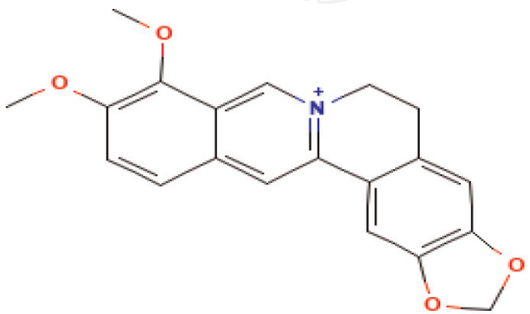
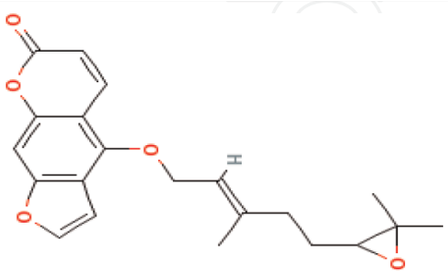
Flavonoids are the main constituent of common edible part of plant, such as fruits, vegetables, nuts, and seeds. These are known to possess various biological activities, such as anti-inflammatory, antioxidant, and antitumor activity, which is now a new

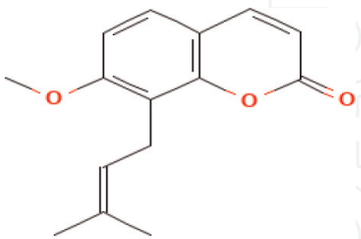
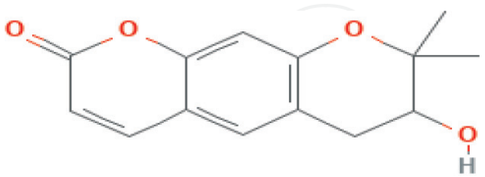
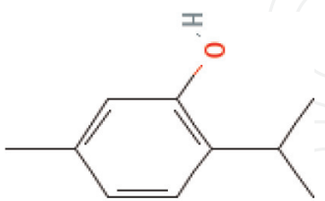
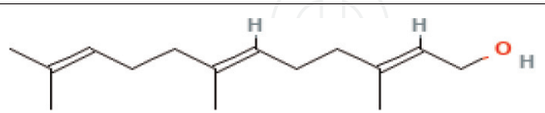
Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
Polyphenols						
Rosa rugosa	 $C_{22}H_{18}O_{11}$	*Beach rose*	Epigallocatechin gallate	Inhibition of swarming motility and biofilm formation	*E. coli*, *P. aeruginosa*	[54]
	 $C_{15}H_{14}O_6$		Epicatechin			
Allium sativum *Arachis hypogaea*	 $C_6H_{10}OS_2$	Garlic	Allicin	Inhibition of biofilms formation, inhibition of expression of bacterial virulence factor and antagonized the activity of LuxR, AhyR, and TraR receptor.	*S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumonia*	[55–57]

Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
	 $C_9H_8O_3$	Peanuts	cis-p-coumaric acid			
Buchanania lanzan Spreng	 $C_7H_6O_5$ or $C_6H_2(OH)_3COOH$	Char, chironji	Gallic acid	Reduction of biofilms formation	*E. coli*, *P. aeruginosa*	[58]
Curcuma longa	 $C_{21}H_{20}O_6$	Turmeric/ haldi	Curcumin	Antimicrobial activity, Biofilm inhibition, Anti-MDR	*S. aureus*, *S. mutans*, *H. pylori*, *A. baumannii*	[59–62]

Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
Terminalia chebula	 $C_{48}H_{28}O_{30}$	Chebulic myrobalan	Terchebulin	Antimicrobial activity or anti-MDR	*A. baumannii*	[63]
	 $C_{41}H_{30}O_{27}$		Chebulagic acid			

Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
	 $C_{41}H_{32}O_{27}$		Chebulinic acid			
Alkaloids						
Piper nigrum L. *Piper longum L.*	 $C_{17}H_{19}NO_3$	Black pepper, long pepper	Piperine	EP inhibitor, delay biofilm formation	MRSA, *C. albicans*	[64, 65]
Sanguinaria canadensis	 $C_{20}H_{14}NO_4^+$	Bloodroots	Sanguinarine	Antimicrobial activity	MRSA	[66]

Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
Coffea arabica, *Theobroma cacao*, *Cola acuminata*, etc.	 $C_8H_{10}N_4O_2$	Coffee beans, cocoa beans, cola nut	Caffeine	Interaction with the quorum sensing proteins and inhibiting biofilm formation	*P. aeruginosa*	[67, 68]
Berberis vulgaris, *Berberis aquifolium*, *Hydrastis canadensis*, etc.	 $C_{20}H_{18}NO_4^+$	Barberry, Oregon grape, Goldenseal	Berberine	Protein and DNA synthesis inhibitor	*E. coli*, *C. albicans*	[69]
Coumarins						
Citrus paradisi	 $C_{21}H_{22}O_5$	Grapefruits	Epoxybergamottin	EB inhibitor	MRSA	[70]

Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
Cnidium monnieri, *Angelica pubescens*	 $C_{15}H_{16}O_3$	Monnier's snow parsley	Osthol	DNA gyrase inhibitor	*B. subtilis*, *S. aureus*, *K. pneumoniae*, MRSA	[71, 72]
Aegle marmelos	 $C_{14}H_{14}O_4$	Bael	Aegelinol	DNA gyrase inhibitor	*S. typhi*, *E. aerogenes*, *E. cloacae*, *S. aureus*	[73]
Terpenes						
Thymus vulgaris	 $C_{10}H_{14}O$	Garden thyme	Thymol	Anti-fungal activity	*Candida* sp. (*C. albicans*, *C. glabrata*, *C. krusei*)	[74]
Cymbopogon nardus, *Cymbopogon citratus*, etc.	 $C_{15}H_{26}O$	Citronella grass, Lemongrass	Farnesol	Cell membrane disturbance	*S. aureus*	[75]

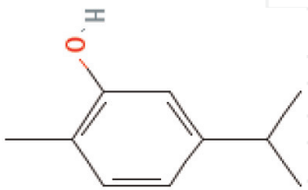
Source	Structures	Common name	Active compounds	Mechanism of action	Activity K/n against	References
Origanum vulgare, *Thymus vulgaris*, *Lepidium flavum etc.*	 $C_{10}H_{14}O$	Oregano, Thyme, pepperwort	Carvacrol	Anti-microbial activity, Biofilm inhibition, Cell membrane disturbance, EP inhibitor	*B. subtilis*, *B. cereus*, *E. coli*, *S. aureus*, *S. enterica*, *S. enteritidis*, *C. perfringens*, *L. monocytogenes P. aeruginosa*	[76]

Table 2.
List of phytochemicals, their source, mode of action, and the sensitive microbe.

therapeutic interest. Flavonoids are the pigments that are responsible for colors in fruits, leaves, and flowers and belong to the polyphenol family. Flavonoids show interesting properties in controlling plant growth and development by interacting in a complex manner with the various plant growth hormones [78].

Flavonoid can be classified on the basis of biosynthesis such as chalcones, flavanones, flavan-3-ols, and flavan-3,4-diols, which are both intermediates in biosynthesis and end products that can accumulate in plant tissues. Other classes are only known as end products of biosynthesis such as anthocyanidins, proanthocyanins, flavones, and flavanols. Two additional classes of flavonoids are those in which the 2-phenyl side chain of flavanone isomerizes to the third position, giving rise to isoflavones and related isoflavonoids. Flavonoids have many medicinal activities; therefore, they have been reported to have many useful properties including anti-inflammatory activity, enzyme inhibition, and antimicrobial activity [79, 80].

4.1.2 Quinones

Quinones are aromatic ring compounds with two ketone substitutions. The major targets of quinones in the microbial cells are cell wall polypeptides, surface-exposed adhesin proteins, and membrane-bound enzymes. Naphthoquinones is one of the largest groups of plant secondary metabolites that exhibit many biological activities.

4.1.3 Tannins

Tannins are found in almost all plant parts, and they possess different antibacterial and antifungal activities. The possible mechanism of antimicrobial efficiency is due to the inactivation of cell envelope transport proteins and microbial adhesins [5].

4.2 Alkaloids

Alkaloids contain variable chemical structures and generally are heterocyclic nitrogen compounds. They tend to exhibit different biological activities, including analgesic effects and antibacterial properties. Therefore, they play a significant role in treating many infectious diseases. The most critical alkaloid groups are aporphines, isoquinolines, quinolones, and phenanthrenes exhibiting suitable antibacterial activities [81]. Their mode of action might be due to the inhibition of repair mechanisms and DNA synthesis, the enzymatic alterations affecting physiological processes, the inhibition of the bacterial nucleic acid and protein synthesis, the modification of the bacterial cell membrane permeability, the damage of the cell membrane and cell wall, the inhibition of bacterial metabolism, and the inhibition of efflux pumps [82–84]. The alkaloids, such as harmane and berberine, results in impaired cell division and ultimately cell death as they possess the ability to intercalate with DNA [85].

4.3 Coumarins

Coumarins are produced naturally by many plants as well as microorganisms, and chemically, they are aromatic benzopyrones, benzene fused with alpha pyrone rings. Some recent studies also have suggested that coumarins are capable of suppressing

quorum-sensing meshwork of bacterial pathogens and affect their ability to form biofilm and virulence factor formations.

4.4 Terpenes

Terpenes are naturally occurring hydrocarbons of either cyclic or open-chain structure, such as sesquiterpenes and monoterpenes. Their oils and compounds have several pharmacological activities, such as antitumor, antiviral, antibacterial, antifungal, anti-inflammatory, antiparasitic, and antioxidant properties [86]. Essential oils (EOs) from medicinal plants have shown anti-QS effects, and EOs produced by aromatic plants have been observed to be effective against biofilms. Preferentially, monoterpenes could impact the membrane structures via increasing the permeability and fluidity, thereby changing the topology of proteins leading to the disturbances in the respiratory chain [87].

5. Conclusion

AMR is becoming a primary cause of morbidity and mortality worldwide, and the resistant microbes are mounting and phenomenal according to the geographic area and the extent of resistance [88]. The infectious agents and diseases that were thought to be controlled by drugs are again emerging with more force against these treatments. The recurrence of resistant microbes, importantly in developing countries, is due to the accessibility of drugs without valid prescription. The golden example is the re-emergence of tuberculosis (in 1980s), which has emerged as multidrug resistant and escalated by HIV infection [89, 90]. The trouble and seriousness in treating MDR strains requires the utilization of a few, some of the time six to seven distinct, drugs. Few mechanisms leading to resistance are the modification of drug targets, the limiting uptake of drug, the active efflux of drug, or the inactivation of drug. Another major well-known resistance mechanism is the biofilm formation.

The protective layers build in the biofilm are a major setback in the treatment of biofilm-related infections, which leads to the ineffectiveness of the existing antibiotics. These layers limit the antibiotic penetration, and thus, the community of sedentary cells survives even in the presence of antibiotics effective against their motile counterparts [53]. Many pieces of evidence suggest that the medicinal plants hold great promise in search of novel antimicrobial agents, and the phytochemicals obtained are very effective in the treatment of infections. Moreover, the plants are cheap, readily available, and almost have minimum side effects. These properties of medicinal plants have gained attention in recent years, for the herbal-based medicines as therapeutics. However, studies are still needed to ensure the safety of antimicrobial phytochemicals and its mechanism of action. Till date, the mechanism of action and the activity related to the structure of phytochemicals have been largely elusive and need further attention [91].

To overcome AMR effectively, all combating new strategies should be practically delivered at all levels, such as community, national, and global levels. Active research to investigate the AMR, its mechanism, strategies to overcome resistance, and leading the novel antimicrobial candidates to clinical practice should be continued. It is important to understand that the distribution, driving force, and the solutions for AMR are different in different countries. Therefore, different approaches are required in high-income countries as compared with low-income countries.

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Conflict of interest

The authors declare no conflict of interest.

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