Chapter

War against ESKAPE Pathogens

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Abstract

Antimicrobial-resistant ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) is regarded to be the prominent reason of Healthcare-Acquired Infections and many among them are multidrug resistant isolates (pathogens that are multidrug resistant (MDR), including vancomycin-resistant enterococci (VRE), carbapenem-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and extended spectrum β-lactamases (ESBL)), and therefore represent a global threat to entire human health. Every year, around 700,000 people deaths are accredited to antimicrobial resistance {AMR}. Devoid of proper feat, the death rate could mount higher to 10 million deaths every year by 2050. Continual usage of antimicrobials aggravated the appearance and widespread of multidrug resistant (MDR) and extensively drug resistant (XDR) bacteria, which leaves even the majority of efficient antibiotics futile. The development of novel antimicrobial agents or other tools to combat these public health challenges is crucial for understanding the mechanism of resistance in these bacteria. To treat these antibiotic-resistant infections, mainly that caused by the ESKAPE pathogens with the advent of novel therapeutics is the need of hour. Substitute therapies such as use of combination of antibiotics or adjuvants with antibiotics, nanoparticles, antimicrobial peptides (AMPs), star polymers, and structurally nanoengineered antimicrobial peptide polymers (SNAPPs) are extensively reported.

Keywords: *Acinetobacter*, *Enterococcus*, *Enterobacter*, *Enterobacterales*, *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, antibiotic resistance, multidrug resistance

1. Introduction

Antimicrobial resistance (AMR) is a wide-ranging global menace and declared by World Health Organization (WHO) as one among top 10 global public health concerns. WHO made a nerve-racking forecast that by the year 2050, infections due to drug-resistance, mainly heightened through the Misuse and overuse of antimicrobials [1], will exterminate approximately 10 million people per annum that will go up in flames of financial catastrophe and in turn entail severe poverty upon millions of people [2]. ESKAPE pathogens are a faction of bacteria including Gram-positive and Gram-negative bacteria, namely, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and

Enterobacter species. With the appearance and widespread of antibiotic-resistant pathogens due to diverse mechanisms of resistance acquired by bacteria, intimidate our capacity to treat infections particularly frightening is the hurried worldwide stretch of multi-resistant and pan-resistant bacteria (also known as "superbugs") causing infections which are untreatable with the already accessible antimicrobials. Bacterial genome analysis made a remarkable conclusion that there is a scarcity of effective antimicrobials as more than 20,000 impending resistant genes have been reported [3] and the number is predictable to be higher in the coming years. In both the developing and developed countries the ESKAPE bug infections are growing in a similar manner [4, 5]. The possible reasons accountable for the widespread of AMR in the community and hospitals is the malnourishment, poor sanitation practices that are responsible for the preamble of antibiotics which are not metabolized into the environmental milieu through animal and human waste [6], unsystematic use of various antibiotics in agricultural practices that comprises of growth promoters and likewise in animal and human medicines [7, 8], in developing countries, the improper regulation over the contradict antibiotics as they are effortlessly accessible without proper medical prescription [9], poor hygienic conditions. Physicians recommend mammoth number of antibiotic combinations devoid of taking into account its side effects. With an over view to combat AMR, the disease which can be treated easily with a single dose antibiotic regimen, is compelled to be treated with high dose combinations to which the bacterium is not susceptible, and the inadequate and overuse of antimicrobial therapy in humans, animal farming, and agriculture is the main driver of AMR [10]. Among ESKAPE pathogens, vancomycin-resistant Enterococcus (VRE), extended-spectrum β-lactamase producing (ESBL) *Escherichia coli,* and methicillin-resistant *Staphylococcus aureus* (MRSA), are frequently seen. And they have gained popularity as they wield resistance in healthcare set-ups against various antimicrobial agents. A correlation of resistance linking the frequency of biofilm formation with host-immune responses has already been recognized [11, 12]. The various resistance conferring mechanisms in bacteria to approximately existing antibiotic classes are extensively studied and described in various literatures [13–15]. The possible mechanisms for resistance include altered permeability of membrane, antibiotic degradation by enzymes, efflux pumps over expression that abolish antimicrobials actively [16–18]. In countries reporting to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the frequency of ciprofloxacin resistance, which is used to treat urinary tract infections, speckled from 4.1% to 79.4% for *Klebsiella pneumoniae* from 8.4% to 92.9% for *Escherichia coli* [19]. In *E. coli*, the Resistance to antibiotic fluoroquinolone, used for urinary tract infections, is extensive [20]. Carbapenem resistant Enterobacteriaceae (i.e., *E. coli, Klebsiella*, etc), responsible for causing life-threatening infections, colistin seems to be the merely last choice treatment [21]. Whilst in several countries, bacteria resistant to colistin causing infections have been detected for which there is no efficient antibiotic treatment at present [22]. In the community as well as in health-care facilities the *Staphylococcus aureus bacteria which is a* component of our skin flora is a general cause of infections. People with drug-sensitive infections are less prone to death as compared to People with methicillin-resistant *Staphylococcus aureus (MRSA*) infections which are 64% more expected to die (WHO report 2021). A new AMR indicator, In the SDG monitoring framework was incorporated in the year 2019, which monitors the rate of various bloodstream infections due to two

distinct antibiotic resistant pathogens: Resistance of *E. coli* to third generation cephalosporins (3GC), and methicillin-resistant *Staphylococcus aureus* (*MRSA*). In 2019, the data provided to GLASS on blood-stream infections owed to MRSA the median rate observed for MRSA was 12.11% (Interquartile Range {IQR} 6.4–26.4) by 25 countries, areas, and territories and the data provided by 49 countries on blood-stream infections due to *E. coli* resistance to cephalosporins third generation was 36.0% (IQR 15.2–63.0) and the data was still at halt to be presented nationally (WHO report 2021). The control and management of gonorrhea is halted by the extensive spread of highly variable and resistant strains *Neisseria gonorrhoeae*, Extended-spectrum cephalosporin (ESC) ceftriaxone which is injectable is the only left behind empiric monotherapy for gonorrhea in various countries [23, 24]. Widespread antibiotic resistance emerged to various classes of antibiotics like penicillins, macrolides, tetracyclines, fluoroquinolones, sulphonamides, and early generation cephalosporins has increased dramatically [6, 25–27]. There is a surge in Antibiotic resistant *Mycobacterium tuberculosis* strains. As per WHO report 2021, 1.5 million people died owing to Tuberculosis (TB). Almost half a million new cases of rifampicin-resistant TB (RR-TB) were identified globally, among which the majority have multi-drug resistant TB (MDR-TB), a form of tuberculosis resistant to the two most potent anti-TB drugs [28]. In present Scenario, at least 700,000 deaths annually are caused due to drug-resistant infections, the World Health Organization published a report in 2019 stating that, if no action is taken, the figure is expected to increase exponentially to 10 million deaths annually by 2050, surpassing cancer, diabetes, and heart disease, as the primary catastrophic cause of death in humans [29]. Hence, stern actions are required to curtail the widespread of strains resistant to antimicrobials as they impose a key challenge to global public health. Therefore, antibiotics in conjunctions, antimicrobial peptides (AMPs), nanomaterials, phages, synthetic chemicals, photodynamic light therapy and integrated multi-omics have been surfaced as an substitute method [30, 31]. AMPs with backbone of amino acids are the host defense peptides which are natural and can be used as a potential alternative candidate to the existing conventional antimicrobials responsible for resistance [32]. Despite of being a powerful weapon to eradicate resistance these AMPs also face drawbacks like: proteolytic susceptibility, toxicity, poor profile of pharmacokinetics, etc. Encapsulating these AMPs in the development of nanomaterials and nanocarriers helps in increasing efficiency of AMPs at the target site and decreasing the cytoxicity and degradation [33, 34]. Due to potential therapeutic efficacy and momentous advantages, structurally nanoengineered antimicrobial peptide polymers (SNAPPs) and the star polymers are used to carry the AMPs [35]. Antimicrobial peptides (AMPs) with diverse mechanisms of action (MOA) and effective antimicrobial activities are measured as significant substitute to solve the problem of multidrug resistance [36].

2. Bacterial structure and antimicrobials mechanism of action

The bacterial cytoplasm is strewn with DNA material and ribosomes, however there are no structured organelles. DNA is single and thread like in appearance, and is compactly folded and organized so that its length which is 1000 times that of the cell itself can be accommodated. DNA gyrase prevents tangling of the DNA

molecule and pedals during DNA replication with regard to folding and supercoiling. Quinolone antibiotics inhibit the DNA synthesis by inhibiting the activity of DNA gyrase; rifampin also hinders the DNA replication process by inhibiting DNA-dependent RNA polymerase [37]. For vital functioning of the cell the chromosomal DNA contains the genetic blueprint; nevertheless, extra chromosomally DNA might also subsist in the cell in the appearance of plasmids. Plasmids are separate from the chromosomes and are circular bodies of double-stranded DNA containing genes that encode for diverse traits, comprising of antimicrobial resistance. In a process of conjugation the plasmids might be transferred from one bacterium to another by means of sex pili [38]. Ribosomes which are nucleoproteins containing the DNA blueprint, allied with long chains of messenger RNA (mRNA) for the process of protein synthesis. In order to allow the amino acids to get linked and initiate protein synthesis, the 30S ribosomal subunit reads the mRNA code, that signals transfer RNA (tRNA) molecules, that carry amino acids, so as to attach to both the 50S and 30S subunits. This process is intervened by the antimicrobials. For instance, 30S subunit gets attached by antibiotic-aminoglycosides so that the erroneous amino acids get inserted into the protein [39]. The 50S ribosomal subunit gets reversibly attached by the macrolides, clindamycin and tetracycline that in turn halt the linking of amino acids. These antibiotics—macrolides, clindamycin and tetracycline are bacteriostatic, even though in some of the bacterial strains macrolides might be bactericidal [40]. The cytoplasm is surrounded by the plasma membrane which acts as the main permeability barrier for the cell. Gram-negative, Gram-positive and fungi all possess this cytoplasmic membrane and rarely few lipophilic, small substances can infiltrate this lipid bilayer, antibiotics—erythromycin and aminoglycosides in order to make their way to ribosomes must cross this lipid bilayer. The cytoplasmic membrane is surrounded by the cell wall that comprises of a sugar (polysaccharide) backbone which is cross-linked by the peptide bonds, the polymer thus formed is mucopeptide, the Peptidoglycan is the precise mucopeptide present in the cell wall. Penicillin-binding proteins and various enzymes that are implicated in synthesis of cell wall are the attachment sites for antibiotic-penicillin [41]. Transpeptidase is the essential PBP, that catalyzes the ultimate cross-link between peptide and sugar in the peptidoglycan molecule, and this cross-link is indispensable for a robust bacterial cell wall. The peptidoglycan and cell wall synthesis is inhibited by β-lactam antibiotics—{cephalosporins, carbapenems, penicillins, monobactams} that bind to the transpeptidase and lead to cell lysis and cell death by triggering the release of bacterial autolysin, are effectual only in opposition to actively dividing bacteria [42, 43]; the tolerance phenomenon wherein mutant bacteria that are lacking autolysins stay susceptible to the β-lactams growth inhibition effect however are resistant to the process of lysis and killing [44]. If antibiotic—tetracycline which is a bacteriostatic agent is given concomitantly, antagonism might be seen. D-alanine gets attached by the vancomycin which is bactericidal against actively dividing bacteria and inhibits the activity of transpeptidase to complete the ultimate cross-linking in the synthesis of peptidoglycan. [45–47]. Cell wall synthesis is also intervened by the antimicrobial—Teicoplanin that get fastened to the nascent Peptidoglycan chain via terminal D-residues, and in this manner inhibiting the cross-linking steps which are crucial for unwavering synthesis of cell wall [48]. When used in combination

with an aminoglycoside, vancomycin becomes effective against *Enterococcus faecalis* [49]. β-lactams and vancomycin which are effective against puncturing of the cell wall are usually synergistic in combination with an aminoglycoside by allowing its way into the cytoplasm so as to target its residues in opposition to enterococci; [50, 51]. The Gram-positive and Gram-negative bacteria diverge in their cell walls as in Gram-negative bacteria there is an extra outer membrane to the cell wall peptidoglycan layer, in Gram-positive bacteria the peptidoglycan layer is thicker; and in Gram-negative bacteria the periplasmic space is present between the cell wall and the outer membrane [52]. Gram-negative bacteria possess the mixed hydrophilic and lipophilic properties in outer membrane that acts as an efficient barricade against various antibiotics. Nevertheless, Porins are the small pores that expand throughout the membrane and permit effortless course for small molecules which are hydrophilic in nature, for instance aminoglycosides, into the periplasmic space. The transport of aminoglycosides across the remaining cell membrane needs electron transport, energy, and oxygen; the absence of these requirements turn bacteria into resistant strain [53]. Likewise, acidic and anaerobic conditions inside abscesses guide towards the less activity of aminoglycosides [48]. The higher the drug concentration of aminoglycosides correlates to efficient rate of microbe killing thus acts as swiftly bactericidal [39]. Gram-negative bacteria is intrinsically resistant to vancomycin which is a big molecule to be passaged via too small porins. The tightly adhered and packed lipopolysaccharide molecules in the outer membrane that turn it somehow hydrophilic obstacles the entry of pencillin like lipophilic molecules. While as amoxicillin and Ampicillin are effectively active against Gram-negative bacteria as they are less lipophilic than penicillin G [54, 55]. Gram-positive bacteria on the contrary are more defenseless to antimicrobial attack as compared to Gram-negative bacteria. β-Lactamase and various exoenzymes that are secreted peripheral to the cell wall of bacteria are inadvertently secreted into the periplasmic space found only in Gram-negative bacteria. The enzyme-β-lactamase will competently render antimicrobial inactive prior to reaching the cell wall as concentration of antimicrobial is low. In this way, Gram-negative bacteria can scrimp and save on the quantity of β-lactamase to be secreted so as to become more effective. On the other side, Gram-positive bacteria should generate large quantities of enzyme, as they secrete the same into the exterior environment, where concentrations of antimicrobial is too high. The folate metabolism is inhibited at two steps by the combinatorial antimicrobial therapy trimethoprim-sulfamethoxazole, that is harmful to bacteria as they need to synthesize their own folate from the precursor—para-aminobenzoic acid [56, 57]. It is postulated that by escalating permeability of bacterial membrane, which renders seepage of bacterial contents, the antimicrobial—polymyxins may exert their inhibitory effects [55]. The daptomycin which is a cyclic lipopeptide causes depolarization of membrane and ultimate death of the bacterium by apparently thrusting its lipophilic tail into the bacterial cell membrane [58]. Hence, the various antimicrobials that are used for the infection treatment caused by bacteria may be categorized according to their key mechanism of actions, and the possible four major modes of action as mentioned aforesaid are as: (i) intervention with synthesis of nucleic acid (ii) inhibition of protein synthesis, (iii) intrusion with synthesis of cell, and (iv) metabolic pathway inhibition (**Figure 1**).

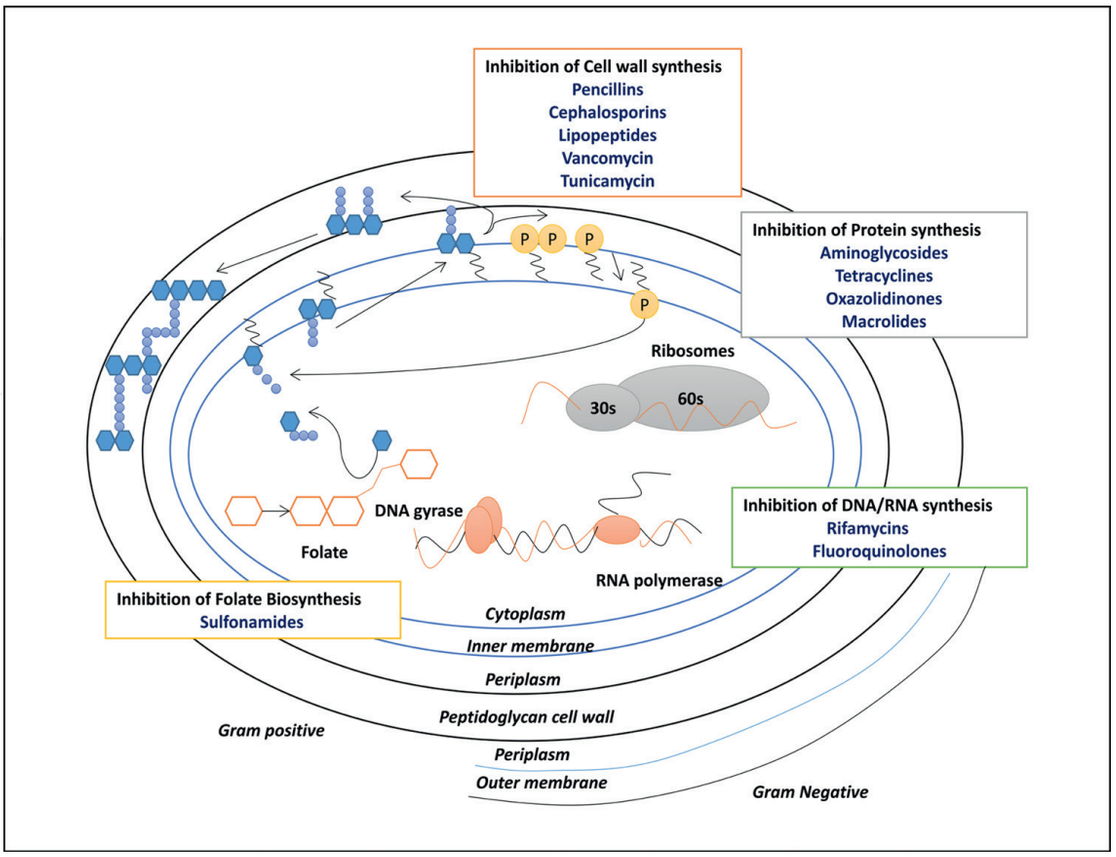

Figure 1.
Schematic representation of major mechanisms of action widely used by antibiotics: antibiotics are medications used to treat bacterial infections. They work by interfering with the growth and reproduction of bacteria, thereby helping the body's immune system to eliminate the infection. There are several major mechanisms of action employed by antibiotics: (i) inhibition of cell wall synthesis: many antibiotics, such as penicillins and cephalosporins, target the synthesis of bacterial cell walls. They inhibit the enzymes involved in building the cell wall, weakening it and causing the bacteria to burst due to osmotic pressure, (ii) inhibition of protein synthesis: antibiotics like macrolides (e.g., erythromycin) and aminoglycosides (e.g., gentamicin) interfere with bacterial protein synthesis. They bind to the bacterial ribosomes, blocking the translation process and preventing the synthesis of essential proteins needed for bacterial growth and reproduction, (iii) inhibition of nucleic acid synthesis: certain antibiotics, such as fluoroquinolones (e.g., ciprofloxacin) and rifampin, target the replication and transcription processes of bacterial DNA or RNA. They interfere with the enzymes involved in nucleic acid synthesis, preventing bacteria from replicating their genetic material and inhibiting their ability to reproduce, (iv) disruption of cell membrane function: some antibiotics, such as polymyxins (e.g., colistin) and daptomycin, disrupt the integrity and function of bacterial cell membranes. They interact with the lipids in the cell membrane, leading to its destabilization and leakage of cellular components, ultimately causing bacterial cell death, (v) inhibition of metabolic pathways: antibiotics like sulfonamides (e.g., sulfamethoxazole) and trimethoprim target specific metabolic pathways in bacteria. They inhibit enzymes involved in the synthesis of essential metabolites, such as folic acid, which bacteria need for survival and reproduction.

3. Antimicrobial resistance: intrinsic, adaptive, and acquired

Bacterial attains antimicrobial resistance and can be as: intrinsic, adaptive, or acquired [59].

3.1 Intrinsic resistance

Intrinsic resistance is the resistance which bacteria can attain due to its inherent properties. For instance impermeability in the outer membrane of Gram-negative bacteria cell envelope is responsible for the glycopepetide resistance. Gram-positive

bacteria are intrinsically less resistant as compared to Gram-negative bacteria due to the presence of outer membrane (OM) in the Gram-negative bacteria, that obstacles the entry of antimicrobials to reach the target site by acting as permeability barrier [58]. Composition of OM, which is an asymmetric bilayer is of phospholipids (internal leaflet), and lipopolysaccharides (LPS, external leaflet) [60, 61]. lipopolysaccharides characteristically includes a short-core oligosaccharide, lipid A, and an O-antigen that can be a stretched polysaccharide. Lipooligosaccharides (LOS) as an alternative of LPS is possessed by some of the Gram-negative microbes for example by members of the genera *Haemophilus*, *Campylobacter jejuni*, *Neisseria.* LPS and LOS share the analogous lipid A structures, but LOS is devoid of the O-antigen units and as such the oligosaccharide is constrained to 10 saccharide units [62]. Small hydrophilic molecules achieve entrance easily via speckled porins on the OM, while as hydrophic molecules passive diffusion is comparably slow. Hydrophilic antimicrobials which are larger in size are debarred efficiently. For example: Despite of being a choice of treatment against methicillin-resistant *S. aureus* (MRSA), Vancomycin—glycopeptide antibiotic which is comparatively larger in size is ineffective against Gram-negative bacteria as it is unable to infringe the Outer membrane permeability barrier. *P. aeruginosa* is resistance against various classes of antimicrobials and also against biocides which are used in disinfectants as it displays number of antibiotic efflux pumps on its surface, additionally the absence of non-specific porins through which antibiotics can permeate via OM [63–67]. Lack of the antibiotic target is the another means of intrinsic resistance to antibiotics. For instance the antibiotics—daptomycin, lipopeptidolactone, which are otherwise effective against vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant enterococci (VRE), and MRSA, so far are ineffective against Gram-negative bacteria [25, 68]. Gram-positive cytoplasmic membrane has considerably elevated fraction of phospholipids which are anionic than that of Gram-negative bacteria; the composition variance lowers the Ca^{2+}-mediated insertion efficiency of daptomycin antibiotic into the cytoplasmic membrane and thereby decreases the bactericidal efficiency of the antibiotic [69, 70].

3.2 Adaptive resistance

Resistance to one or more antimicrobial agents that is induced by the various environmental stimuli (e.g., nutrient conditions, pH, stress, growth state, sub-inhibitory levels of antibiotics, concentrations of ions). Adaptive resistance is transitory on contrary to intrinsic and acquired resistance. Once the inducing stimuli is impassive, adaptive resistance allows bacteria to react more hastily to the antimicrobial challenges, and usually reverts it back to the original state [59, 71–73].

Adaptive resistance is probably the outcome of epigenetic changes, those results from the change in the gene expression in retort to the changes in environment which in turn is responsible for the formation of irreversible phenotypes. For adaptive resistance to take place, it has been proposed that DAM methylase causing DNA methylation which is responsible for various gene expression profiles that are diverse in the bacterial population and possibly provide epigenetic inheritance of gene expression and heterogeneity for the occurrence of adaptive resistance [71, 74]. Meticulously, modulation in the porins and in the expression of efflux pumps have been concerned with the appearance of adaptive resistance [71, 75]. The elevated resistance with regard to the environmental signal might possibly not be reversed once the signal is retrieved and leads to the steady enhancement of minimum

inhibitory concentration (MIC) with time, when comparing the differences in the effectiveness of an antibiotic *in vitro* and *in vivo*, the adaptive resistance phenomenon may be responsible for the same and can be involved in the antimicrobial treatment failure in the clinics [16, 76]. The capability of microbial populations to propagate in the existence of antimicrobials sub-inhibitory levels via adaptive resistance may permit for enduring and efficient mechanisms of resistance to develop [26, 73]. In response to the external environmental changes the bacteria are facilitated to modify their behavior by the extra mechanisms of adaptive resistance, which is more seen in the persister and biofilm development. Quorum sensing process that is driven by the secretion of various small signaling molecules that allows the microbes to commune is the driver for the biofilm formation. Bacteria are much more resistant within a Biofilm when compared to the free swimming bacteria [77]. If, for instance the initial signal may possibly be approximately translated as: "Is there anybody?", the succeeding revealing of a suitable quorum (cell density) would elicit a amend in the memo to: "Let's reconcile downward and structure a population". At this stage, the bacteria will underwent a significant change from the free swimming, planktonic form distinctive of an acute infection, to the Biofilm mode found in chronic and infections (device-related) due to altered gene expression [78, 79]. In comparison to planktonic microorganism the biofilms which are attached to the surface, and sheathed by a polymer matrix, as whole communities of microorganisms, leave bacteria thousand times more resistant to antimicrobials [77, 80]. Biofilms allows the microorganisms to withstand in exceptionally callous environments as they become more resistant to host immune defenses, biocides, and sheer force [81]. The capability of antimicrobials to inhibit the required cellular proteins for microbial growth is reduced in the subpopulations of cells referred as persisters that stop dividing actively and enter into a quiescent state [82].

3.3 Acquired resistance

A bacterium attains resistance by either mutation or via horizontal gene transfer—from an exogenous source the attainment of new genetic material. The three mechanisms by which horizontal gene transfer can occur [16, 83]. (i) Conjugation: is almost certainly imperative mechanism of horizontal gene transfer. The genetic material is transferred from one cell to another by sex pillus formation by which plasmid is taken by recipient cell from the donor cells. Single plasmid has assembly of various multiple resistance genes that are mediated by mobile genetic elements (integrons, Insertion Sequence Common Region—ISCR-elements, and transposons). In a single conjugation incident these multiple resistant genes facilitate the transport of multidrug resistance. (ii) Transduction: the transfer of the genetic material is transferred among a recipient and donor bacterium by a bacteriophage. (iii) Transformation: In a recipient bacterium Free DNA fragments from a dead bacterium enter and get integrated into its chromosome via genetic recombination. Rarely bacteria are transformable naturally.

Gram-negative bacteria also exhibit explicit acquired molecular mechanisms of resistance to antibiotics [6, 84]. These are classified as: (1) inactivation/modification of antibiotic, (2) abridged antibiotic uptake, (3) antibiotic target alteration, (4) augmented antibiotic efflux. To provide high level of resistance against a specific antimicrobial, in maximum incidents, more than a few of these mechanisms coalesce (**Figure 2**).

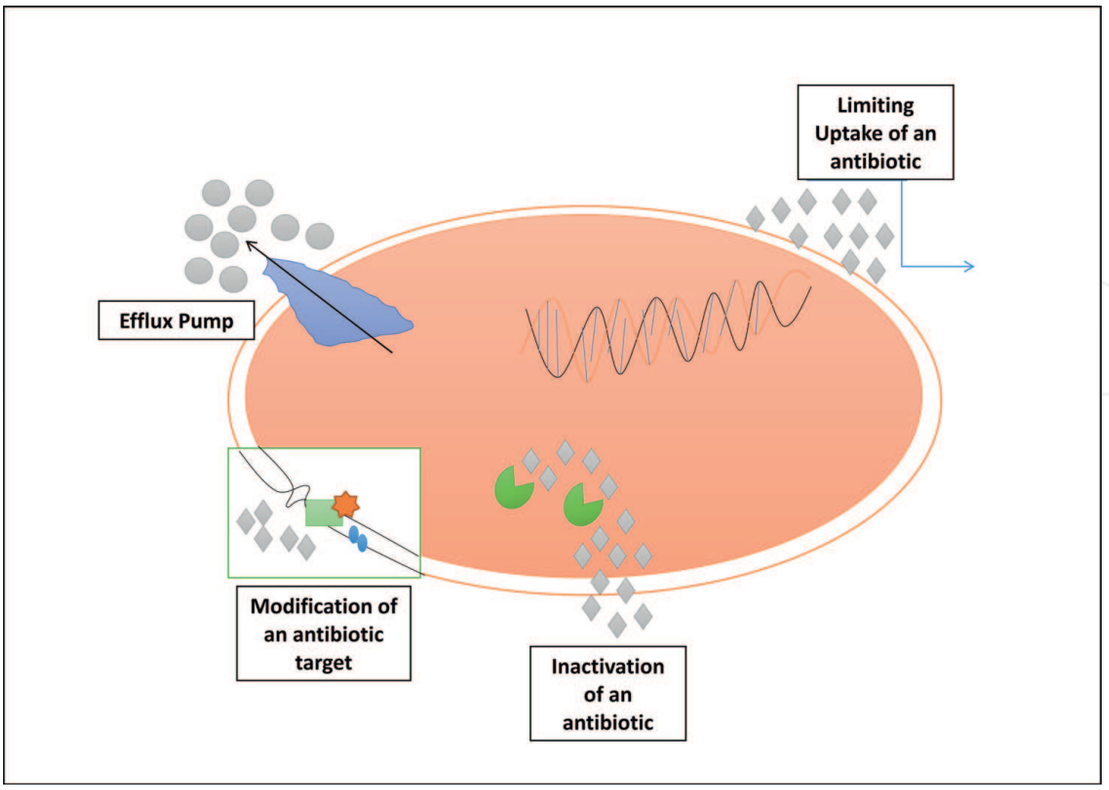

Figure 2.
Schematic representation of general antibiotic resistance mechanisms: antibiotic resistance is a phenomenon where bacteria and other microorganisms develop the ability to withstand the effects of antibiotics. There are several mechanisms through which bacteria can acquire antibiotic resistance. Here are some of the common mechanisms: (i) mutation: bacteria can undergo genetic mutations that result in changes to their DNA, including genes responsible for antibiotic susceptibility. These mutations can alter the target site of the antibiotic, making it less effective. Additionally, mutations can lead to the production of enzymes that inactivate or modify the antibiotic, rendering it ineffective, (ii) efflux pumps: bacteria can possess efflux pumps, which are specialized proteins that pump antibiotics out of the bacterial cell before they can exert their effect. These pumps act as a defense mechanism by expelling the antibiotic from the cell, reducing its concentration and rendering it less effective, (iii) enzymatic inactivation: bacteria can produce enzymes that chemically modify or degrade antibiotics, rendering them inactive. For example, β-lactamase enzymes are responsible for the breakdown of β-lactam antibiotics, such as penicillins and cephalosporins, (IV) altered permeability: bacteria can modify the structure of their outer membrane or cell wall, reducing the permeability of antibiotics into the cell. This prevents the antibiotics from reaching their target sites and reduces their effectiveness.

4. Inactivation of antimicrobials: hydrolysis of β-lactam antibiotics is catalyzed by β-lactamase enzymes

The most often prescribed antibiotics are β-lactams. These antibiotics inhibit the cell wall synthesis by inhibiting the transpeptidase enzymes (penicillin binding proteins; PBPs) that are involved in peptidoglycan strand cross-linking. Autolytic endogenous enzymes under these circumstances are activated via a two-component system VncR/S {is one of the two component systems (TCSs) and is composed of a response regulator 'VncR' and a sensor histidine kinase 'VncS'}, which predisposes the bacterial cell towards osmotic rupture and destabilizes the cell wall [85]. β-Lactam ring is an essential component of β-lactam antibiotics. β-Lactamase enzymes render this ring (four-membered) of β-lactam antibiotics prone to deactivation and hydrolysis so as to overcome these antibiotics. β-Lactamase enzymes are having different activity profiles and are highly diversified. The chief categories of these enzymes are

carbapenems, cephalosporins, monobactams, penicillins, and cephamycins [84]. Regrettably, β-lactam antibiotics resistance is prevalent and escalating swiftly. New Delhi metallo-β-lactamase 1{NDM-1}, is the recently discovered β-lactamase enzyme that is capable of rendering inactive the last line of carbapenem antimicrobials and is almost resistant to all β-lactam antibiotics. NDM-1 is contemplated to have its origin from New Delhi and its swift wide-reaching spread was precipitated by medical tourism [86, 87]. β-Lactam antibiotics are now frequently used in combination with β-lactamase inhibitors (sulbactam, tazobactam, and clavulanate) with an aim to combat the widespread increased issue of bacterial β-lactamases so as to protect the β-lactam antibiotics from hydrolysis and subsequent deactivation [88].

5. Antimicrobial efflux: antibiotic efflux pumps lessen the level of antibiotics inside the cell

Antibiotic efflux pumps are proteins that act by reducing the concentration of antibiotic to sublethal/subtoxic levels by extruding antibiotics from the bacterial cell (periplasm), an intriguing characteristic feature of these efflux pumps is their capability to extrude an extensive variety of different compounds that are structurally diverse [65, 89–92]. This substrate promiscuity is the ensuing development of multidrug resistance in clinical aspects [65, 66, 93, 94]. Antibiotic efflux pump is recognized as the first line defense of the cell mainly in the adverse conditions wherein bacteria is challenged with an antibiotic, the momentary up-regulatory expression of efflux pumps takes place, which lowers the concentration of antibiotic to sub-lethal levels in the cell, which permits the cell survival till a particular mechanism of resistance is achieved. As a result, an active drug efflux pump is mutually sufficient and necessary for the selection of novel drug-resistant mutations [95–98]. Clinically pertinent levels of AMR are conferred by efflux pumps of the resistance-nodulation division (RND) family in Gram-negative bacteria [15, 65, 99]. In Gram-negative bacteria, these span the outer membrane (OM), periplasm, and the inner membrane (IM) to extrude the antibiotics and are complexes as protein assemblies—tripartite in nature [100]. The tripartite drug efflux complexes: MexA-MexB-OprM and AcrA-AcrB-TolC transporters from *P. aeruginosa* and *E. coli* respectively, are the best-studied. The outer membrane proteins TolC/OprM, permit the antibiotic to get transported to the outside of the cell, and the inner membrane fusion proteins AcrB/MexB, also referred as periplasmic adaptor proteins drive out antibiotics from the periplasm or from the cytoplasm by make the most of the proton motive force [100–102].

6. Distorted outer membrane permeability—drop in antibiotic uptake

The dissemination of small hydrophilic antibiotics, for example β-lactams, via outer membrane (OM) of Gram-negative bacteria occurs through porins [103]. As the OM of Gram-negative bacteria acts as first line of defense and permeability barricade. These porins are characterized by a pore {aβ-barrel structural motif} with a inner region which is hydrophilic in nature. Porins either wield substrate specificity or are diffusion porins (non-specific). For instance: ferric enterobactin protein (FepA), which is an iron acquisition porin possess an extra 'plug' domain, which autonomously increases the conscription of the precise cargo [104]. On the basis of interaction and size of the molecule/compound with an inwardly folded loop (loop 3)

which contains charged residues, the diffusion porins are capable to limit cargo [61, 75, 105]. For the intrinsic level of antimicrobial resistance in Gram-negative bacteria the properties of constitutively articulated porins are immensely important. For instance: intrinsic level of resistance to a variety of distinctive antibiotics in *P. aeruginosa is* much higher as compared to the Enterobacteriaceae. As *P. aeruginosa* expresses 'slow' porins with condensed diffusion rates and does not produce lofty permeability classical porins [61]. *P. aeruginosa* expresses numerous explicit porins due to its large genome size, these explicit porins permit the diffusion of small, definite nutrients, while as antibiotics which are bulkier-{Cephalosporins} are not allowed to pass through, and are deactivated by β-lactamase hydrolysis after developing insensitivity [105].

Porins can develop acquired resistance through these possible mechanisms: (i) mutations that renders non-functional via various modifications (for instance: in PenB porin, the amassing of two negatively charged amino acids in the channel-constricting loop 3 of *N. gonorrhoeae* consequences out in drastically condensed permeation of antibiotic-{penicillin} [61, 105, 106]. (ii) Mutations down-regulating the porin expression (for instance: β-lactam resistance to *E. coli* is conferred by the loss of OmpF), and (iii) substitution of small channel size porin with large sized porin (for instance: OmpK36 replaces the large channel porin OmpK35 and is responsible the *K. pneumoniae* isolates resistance to various β-lactams.

In AMR, there is a considerable relationship linking antibiotic-efflux and reduced outer membrane permeability. Collectively, these two mechanisms impart resistance to various classes of antimicrobials such as aminoglycosides, choloramphenicol, erythromycins, tetracyclines fluoroquinolones, etc. Nevertheless, antimicrobial resistance is frequently multi-dimensional, and relies on various molecular mechanisms that operate concurrently. Increased antibiotic efflux and reduced permeability together with the various mechanisms such as target alteration and drug modification confers antimicrobial resistance to the antibiotics mentioned above.

6.1 Antimicrobial modification

Alteration by enzyme alteration of the antibiotic-aminoglycoside is an imperative example of antibiotic modification that is currently the common mechanism of resistance clinically. Gram-negative bacteria (*A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae* ssp.,) causing infections are treated clinically by aminoglycoside as in treatment of carbapenem-resistant Enterobacteriaceae ssp. causing uncomplicated Urinary Tract Infections [107]. Aminoglycosides act by binding to the 30S ribosomal subunits, 16S rRNA-aminoacyl site where it leads to the misinterpretation of the genetic code and translation inhibition and interferes with the protein synthesis and thereby exert antimicrobial activity [108, 109]. Nevertheless, the aminoglycoside structure left them susceptible to alterations by various enzymes such as aminoglycoside *O*-nucleotidyltransferases (ANTs), aminoglycoside *O*-phosphotransferases (APHs), and aminoglycoside *N*-acetyltransferases (AACs), that can alter the antimicrobial and render it ineffective [110]. The consequential altered antibiotic wherein various aminoglycoside modifying enzymes (AMEs) intercede adenylation, phosphorylation, or aminoglycoside acetylation rendered aminoglycoside with decreased target avidity. AMEs are encoded by genes which are generally positioned in mobile genetic elements (MGEs) allowing them to competently disseminate among bacteria. Through this mechanism, almost all medically significant bacteria can reveal resistance to aminoglycoside [111]. Chloramphenicol resistance is mainly inferred by

the enzymatic acetylation of the antibiotic. In an extensive range of bacterial species various chloramphenicol acetyltransferases (CATs) have been described [112].

6.2 Antibiotic target alteration

When antibiotic has no longer any activity against target as the antibiotics target is changed it is referred as—target alteration. Various classes of antibiotic resistance are caused by this mechanism and are very common. Gram-negative and Gram-positive resistant bacterial strains causing infections are treated nowadays with fourth-generation fluoroquinolones [113]. Here we will discuss the alteration of the target of fluoroquinolones antibiotic. Epidemiological verification suggests a sturdy association between resistance to antibiotic—fluoroquinolones and various other exigent resistance phenotypes. (e.g., *K. pneumoniae* are concurrently resistant to fluoroquinolones producing elevated levels of extended-spectrum β-lactamase (ESBL) [114]. These antibiotics target vital bacterial enzymes, exclusively type II topoisomerases (topoisomerase IV and gyrase) therefore, intervening with the process of DNA replication.

Fluoroquinolones result in the fragmentation of DNA and eventually cell death by interacting with the DNA–topoisomerase complex [115]. Fluoroquinolone affinity for binding is altered by the mutations in the genes *gyrA and gyrB-* (particularly *gyrA*) that led to the substitution of amino acids in the structure of proteins and results in drug resistance [116, 117]. The chromosomal mutations in the bacterial topoisomerase IV and/or gyrase genes is the cause of Quinolone resistance [117].

Likewise the commonest mechanism for resistance to linezolid is due to the gene mutation encoding the domain V of the 23SrRNA. The add up of the alleles which are mutated correlates with the raise in Minimum Inhibitory Concentration (MIC), as bacteria possess various copies of the 23SrRNA genes. Linezolid resistance has been also related to the mutations in L3 and L4 {ribosomal proteins} which margin the binding site of antibiotic—linezolid [118]. In the development of resistance to various antibiotics—streptogramin B, lincosamide and, macrolide, implication of 23SrRNA mutations have been reported [119]. The resistance in the β subunit gene of RNA polymerase is typically accountable for resistance to rifampicin [120, 121]. Similarly, in various bacteria which are of clinical importance, the resistance to sulfonamides, and trimethoprim is due to the recombinational changes/mutations in the dihydropteroate synthase (DHPS) gene or the dihydrofolate reductase (DHFR) gene respectively [122]. Resistance to antibiotics—clindamycin, linezolid, and chloramphenicol is due to the 23SrRNA methylation by an enzyme which is encoded by the cfr gene [18, 112, 123]. Cross-resistance to lincosamides, macrolides, and streptogramin B is due to the 23SrRNA methylation by enzymes, which are encoded by a number of erythromycin ribosome methylase {erm} genes [119].

7. Strategies to combat antimicrobial resistance include

7.1 Use of non-essential target inhibitors

To date, among the various promising approaches that are used to curtail the antibiotic resistance is using antibiotic adjuvants which will hit targets that are non-essential in bacteria. There is a decline in investment by various pharmaceutical companies with regard to the new antibiotic drug discovery in the last few years [124].

The scientific challenges strive towards the fact that since the "golden age" just two new antibiotic classes have made their way into the clinics. Numerous bacteria by now possess the resistance mechanisms against the diverse antibiotics which are in the developmental phase are derivatives of previously accepted antibiotics [125]. To target non-essential pathways so as to reduce the rate of antibiotic resistance the promising success has been achieved with the combinatorial approach of antibiotics or with antibiotic "adjuvants" [126]. Drug combinations and synergy are coming up as appealing line of attack against MDR bacteria and possibly protect the existing antibiotics via the use of adjuvants. Amoxicillin and clavulanic acid combination is so far success story wherein clavulanic acid acts as β-lactamases inhibitor having fragile antibacterial activity and Amoxicillin is an effective β-lactam rendered inactive by β-lactamases, The Augmentin, that was the preeminent-selling antibiotic in 2001 is a result of this union comprising of an antibiotic "adjuvant" together with an antibiotic. Antibiotic adjuvants are molecules that are capable to improve the antibiotic activity thereby minimizing or jamming the mechanism of resistance though they are themselves with fragile or no antibacterial activity. These can expand the antibiotics spectrum of activity by suppressing the intrinsic resistance. In literature, it has been reported that the Gram-negative bacteria causing infections are treated by the usage of Gram-positive selective antibiotics. Where toxicity is a concern this proves to be a good strategy (e.g., colistin). Antibiotic adjuvants render antibiotic molecules potent even at lower doses via enhancing the bacterial susceptibility [127]. Till date, to obstruct the antibiotic resistance three main antibiotic adjuvants have been developed:

7.1.1 Efflux pumps inhibitors {EPIs}

Efflux pumps inhibitors {EPIs} are tiny molecules which are capable to fasten efflux pumps and obstruct their extrusion movement. Efflux pumps can be inhibited by adding drug substrate with new functional group that will impede detection, Intervening with the expression of efflux gene, ability to obstruct the channel and transfer machinery of the pump is disjoined [128, 129]. Various studies that are carried so as to recognize the substrates of efflux pumps and their inhibitors. From accessible antibiotics, the first EPIs were discovered accidentally, the reserpine is the popular one that inhibit the NorA multi-drug transporters, lowering the MIC values by elevating the fluoroquinolone intracellular concentration [130].

Till date, MP-601, is the only documented inhibitor that is presently administered in patients with cystic fibrosis or ventilator-associated pneumonia or as an aerosol [131, 132]. Dipeptide amide, named phenylalanine-arginine-β-naphthylamide is the EPI lead compound that inhibits numerous but not all RND efflux pumps. In ample range of bacteria this have been found to enhance or restore the activities of diverse classes of antimicrobials, which comprises of chloramphenicol, 4-fluoroquinolones, and macrolides [133]. Nevertheless, phenylalanine-arginine-β-naphthylamide and its derivatives are toxic to be included in therapy [134]. Phenothiazine derivatives are other molecules with efflux pumps' inhibition activity and various efforts have been employed to optimize them for therapeutics, phenothiazines enhanced the antibiotic activity of various classes, counting azithromycin, erythromycin, and levofloxacin. This EPIs class are allied to interfere at the inner membrane of the bacteria with the proton gradient [135]. Both *in vitro* and *in vivo*, *M. tuberculosis* efflux pumps activity has been reported to be inhibited by EPIs [136]. Thioridazine (TZ) derivatives with already known anti-tuberculosis drugs, showed efflux inhibitor activity jointly with

the synergistic effect both *in vitro* and with human monocyte-derived macrophages which are infected. In multi-drug-resistant bacterial isolates, Quinolines showed antibiotic efflux inhibition. Certainly, it has been shown that several quinoline derivatives are competent of enhancing the Antibiotic activity via the efflux transporters inactivation: AcrAB-ToIC (RND family) [137]. Studies reported, this class of compound showed synergy with antibiotics: including chloramphenicol, tetracycline, and norfloxacin, in Gram-negatives isolates of *E. aerogenes* and *K. pneumoniae* [138]. In salmonella enterica, chlorpromazine also inhibits AcrB, by indirectly exerting synergistic activity by modulating acrB gene expression [139].

Consequently, it is promising to substantiate that efflux inhibition might direct to a multiplicity of optimistic results by: (i) enhancing the activity of antibacterial drugs subjected to efflux, (ii) maintenance of the antibiotic concentration at the remedial dose, and (iii) reducing the treatment period by limiting multi-drug tolerance [140, 141].

7.1.2 β-Lactamase inhibitors

Antibiotic penicillin hydrolysis by enzyme lactamases was the first mechanism of lactam resistance reported in Gram-positive bacteria. Lactam antibiotics mechanism of action involves the transpeptidases inactivation which is utmost for the final biosynthesis of cell wall in bacteria. In order to protect the cell wall, bacteria synthesize the lactamases that are capable for hydrolyzing lactam-based antibiotics and the degree of hydrolysis depends on the form and β-lactamases number formed by the bacteria. For antibiotic activity the key element is the β-lactam ring, for the reason of its electrophilicity, for acylating the penicillin-binding proteins (PBPs) irreversibly. PBPs are accountable for peptidoglycan synthesis that is liable for maintenance of the bacterial cell wall structural integrity. Till date, discovery of hundreds of β-lactamases are capable with identical action. The difference in affinity for various substrates is due to difference in their amino acid sequences. Commonly, two different methods for the classification of β-lactamases are: one is based on characterization of structures-Ambler classification and, the other one is based on a functional characterization—Bush and Jacoby classification [142, 143]. In therapeutic, several β-lactams antibiotics are used and has led to the synthesis of specific β-lactamases class, referred as extended-spectrum β-lactamases (ESBL), that hydrolyzes maximum β-lactam antimicrobials, and are particularly delineated in Enterobacteriaceae-{including *K. pneumoniae*, *P. mirabilis*, and *E. coli*} [144]. The family of β-lactamases, which are most versatile with broader spectrum activity and these β-lactamases identify approximately all hydrolysable β-lactams, while as most are resistant to the inhibition by all viable commercially β-lactamase inhibitors [145]. In order to surmount the β-lactamase-mediated resistance to β-lactams, two possible strategies are opted: (i) selective β-lactamase inhibitors (BLIs) developed and to be used in combination with a β-lactam antibiotic, and (ii) development of stable β-lactamase—antibiotics {e.g., carbapenems and cephalosporins which are stable towards β-lactamases hydrolysis [146]. The significant step in the antibacterial discovery field is the discovery of *Streptomyces clavuligerus* secondary metabolite—clavulanic acid, which is able to inactivate many β-lactamases, therefore, the association of amoxicillin and clavulanic acid is the first development in the β-lactam-β-lactamase inhibitor amalgamation in the form of Augmentin, [147] further led by the prefacing of other combinations.

After the clavulanic acid discovery, a crusade in medicinal chemistry was initiated with an aim to synthesize various penicillanic acid sulfones having inhibitory activity

against β-lactamase. Tazobactam and sulbactam among these were commercialized productively. Both possess the similar activity spectrum as that of clavulanic acid. In combination with piperacillin, tazobactam is used with the recent ceftolozane and cefoperazone for nosocomial infections, comprising the ones caused by MDR *P. aeruginosa* [148]. For worldwide use, ampicillin and sulbactam is combined and an additional synergy against anaerobic bacteria is achieved with cefoperazoe [149, 150]. These compounds in broad if administered alone do not show any antibacterial activity. With some exceptions MIC of clavulanic acid alone against *N. gonorrhoeae* is 1 μg/mL [151]. Sulbactam is ineffective against MDR strains and has MIC in the range of 10 and <8 μg/mL against wild-type *Burkholderia cepacian* and *Acinetobacter spp.* respectively [152]. After two decades of space, following the discovery of β-lactamase inhibitors, a new class of non-β-lactam β-lactamase inhibitors arose, which are based on the diazabicyclooctane (DBO) scaffold, avibactam is the first inhibitor from this class which possess higher activity spectrum in comparison with clavulanic acid, and approved for therapeutic usage with ceftazidime in combination. Likewise, the combination development (e.g., aztreonam-avibactam or ceftaroline-avibactam combinations) is ongoing [88, 153, 154]. In combination with Imipenem, relebactam (MK7655, 23) and Nacubactam (RG6080, 22) are DBOs under development. The relebactam activity is same as that of avibactam spectrum of activity [155]. RG6080 (formerly OP0565) like other DBOs is having inhibitory spectrum of activity and against enteric bacteria also exhibits some intrinsic antibacterial activity [156]. To target microbes synthesizing carbapenemases, synthetic non β-lactam β-lactamase inhibitors, a new class of inhibitors that are made up of boronic acids including RPX7009 in combination with meropenem is developed. Widespread β-lactams resistance in on surge, particularly in Gram-negative organisms [157–159].

At the present time, to tackle the resistance developing new β-lactamase inhibitors is the most pursuing challenge which will endow with defense for the almost many antibiotics that are used in clinical therapeutics, at least for the current time.

7.1.3 Baiting outer membrane: {outer membrane permeabilizers}

Specifically, the antibiotics hit target(s) inside the cells, exerting their antimicrobial action in therapy that is used presently. Outer membrane which acts as the defense, shelter the Gram-negative bacteria and is composed of porins and polyanionic lipopolysaccharides, which hinders the entry of xenobiotics antibiotics, as a result of complex wall that is responsible for reduced efficacy of antibacterials, at the outer membrane level mostly stirring strains which are resistant generally adopt mutation in proteins, Therefore, there is a need to develop the antibiotics that pass through the bacterial membrane [105]. In this regard, to deal with the bacterial resistance, the outer membrane (OM) acts as a potential target, ability to develop new effective classes of antibiotics can be enhanced by knowing the bacterial cell wall [160].

Depending on the small molecules chemical nature, the antibiotics use two strategies to penetrate the bacterial cell wall: (i) antibiotics {e.g., β-lactams, phenicol antibiotics, and fluoroquinolones) are hydrophilic molecules that take benefit of their capability to interact with peculiar porins and diffuse via active transport mechanism; (ii) antibiotics {e.g., rifampicin and macrolides} are transported via mechanism of passive transport across the lipid bilayer [61, 105].

A new strategy to improve the antibiotic entrance capacity is the use of permeabilizers that act as antibiotic adjuvants to enhance the permeability membrane

propensity. Permeabilizers act by capturing cations in the outer layer, and interacts with polyanionic lipopolysaccharides and thereby destabilizes the bacterial membrane wall. As a result the OM can be easily crossed over by xenobiotics {antibiotic}. Polymyxin—for instance polymyxin-B, cationic peptides, aminoglycosides, colistin, polyamines, or cationic cholic acid derivatives, are membrane permeabilizers [161, 162]. New substitute strategies for designing novel small molecules that can enhance antibiotic dissemination across the membrane, and increasing intracellular concentration, is in great demand [163]. With regard to same, various chemosensitizers (e.g., antimicrobial peptides, surfactants, detergents, etc.) have been proposed that are enable to interrupt protein activities in the membrane (e.g., membrane channels and porins) [164, 165]. In order to fight with resistant strains, the classical antibiotics are used in combination and administered with these classes of antibiotic "adjuvant" [166, 167]. It has been reported recently that on *E. coli* membrane, glycine basic peptide (GBP) exhibits concentration dependent antibacterial activity and leads to cell fragmentation, GBP is a cationic peptide that works by disturbing the ion-channel and membrane barrier of *E. coli*, which results in the ion loss {Mg^{2+}, Ca^{2+}, and K^{+}} and also enhanced the susceptibility of *E. coli* to rifampicin and erythromycin which are otherwise unable to cross the OM of Gram-negative bacteria [168]. The menadione in another study revealed that in combination with aminoglycoside class of antibiotics it showed synergy and reduced the MIC of these antibiotics [169].

7.2 Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are interesting antibiotic class which is endowed with antibiotic adjuvant potential. Multicellular organisms naturally produce peptides (AMPs) which are amphiphilic in nature comparatively small in size (10–50 amino acids) with cationic charge and acts against pathogenic bacteria during infections as the first line of defense in opposition to microbes. AMPs proposed mechanism of action is their capability of forming amphipathic α-helix or short β-sheet structures, thereby destabilizing the bacterial outer membrane [170, 171]. AMPs cationic residues forms the electrostatic interaction with the bacterial anionic cell wall and targets it by diverse mechanisms so as to obstruct and hamper the development of resistance. It also leads to the disintegration or permeabilization of the bacterial cell wall by insertion of hydrophilic subunits. They also form pores on the bacterial membrane and leads to the death of microbe [172, 173]. The cationic short amphipathic antimicrobial peptides act by immunomodulatory action and direct cell killing. The three crucial steps that are involved in AMP mediated cell killing are as attraction, attachment, and insertion of peptide. The process of attraction is electrostatic in nature between the negatively charged surfaces units and charged anionic/cationic peptides. The bacterial polysaccharide surface must be infiltrated by these peptides and adhere with the teichoic and lipoteichoic acid from Gram-positive bacteria or lipopolysaccharide from the Gram-negative bacteria in the attachment step. Attachment is followed by the peptide insertion. AMPs cause cell membrane disintegration by pore formation in the bacterial cell membrane and are explained by {The 'Carpet model', 'Barrel-stave' and 'Toroidal-pore'} (**Figure 3**) [174]. Negatively charged cell membrane and the peptides are electrostatically bonded and is spread all over in the 'Carpet model,' (**Figure 3a**). The lipidic fraction is aligned by the hydrophobic region, the inside portion of pore is hydrophilic in the 'Barrel-stave' model (**Figure 3b**). The peptides which penetrate leads towards lipidic portion twisting so as to give a structure of pore in the 'Toroidal pore' model (**Figure 3c**) [175]. By metabolic modulators, intracellular killing activity

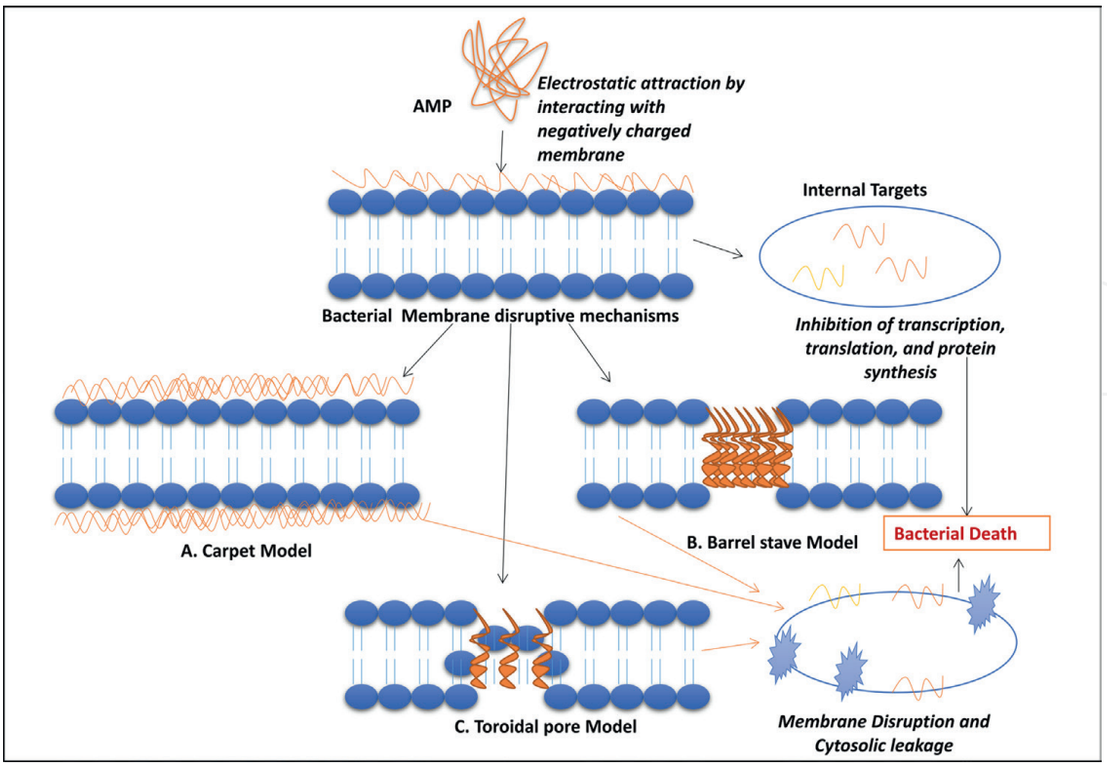

Figure 3.
Schematic representation of membrane disruptive and non-membrane disruptive mechanisms of antimicrobial peptides (AMPs): a. Carpet model: in the carpet model, AMPs bind to the surface of microbial membranes and disrupt their integrity by forming a "carpet" of peptides. This disrupts the packing of lipids in the membrane, leading to the formation of transient pores. The carpet model suggests that the peptides do not form well-defined channels but rather cover the membrane surface, causing leakage of intracellular components and ultimately cell death. b. Barrel stave model: according to the barrel stave model, AMPs insert themselves into the lipid bilayer of the microbial membrane to form transmembrane channels. The peptides assemble together in a "barrel" fashion, with their hydrophobic regions embedded in the lipid bilayer and their hydrophilic regions facing the aqueous environment. This model suggests that the peptides create stable channels that span the membrane, allowing ions and molecules to flow across. The channels formed by the peptides disrupt the membrane's electrochemical balance, leading to cell death. c. Toroidal pore model: the toroidal pore model proposes that AMPs induce the formation of toroidal pores in the microbial membrane. In this model, the peptides interact with the lipid bilayer, causing local curvature and bending of the membrane. The peptides form a toroidal structure, where both the peptides and the lipid head groups curve inward, creating a pore-like structure. This pore allows the passage of ions and molecules, disrupting the membrane potential and leading to cell death. It's important to note that these models represent simplified representations of the complex interactions between AMPs and microbial membranes. The exact mechanisms of action may vary depending on the specific AMP and the target microorganism. Additionally, recent research suggests that multiple models may operate simultaneously or in a sequential manner to exert the antimicrobial effects of AMPs. These models provide valuable insights into how AMPs function and can aid in the design and development of new antimicrobial therapies. However, it's important to continue research in this field to gain a deeper understanding of the intricacies of AMP-membrane interactions.

is exerted by AMPs. These activate bacterial apopotosis behavior by autolysin upregulation {e.g., N-acetylmuramoyl-L-alanine} via acting as DNA replication modulators—Buforin II, Inhibition of enzymatic activity by drosocin, apidaecin, histatins, Inhibition of DNA, RNA, and synthesis of protein by pleurocidin, dermaseptin, Human Neutrophil Peptide-1 (HNP-1), Human Neutrophil Peptide-2 (HNP-2). Bacteria are showing resistance to AMPs, similar to the conventional antimicrobials through the mechanism of cell surface bacterial alteration via discharging enzymes that are proteolytic and thereby results in the hydrolysis of peptides {for instance: by forming capsular body *K. pneumoniae* hinders the AMPs penetration, and by incorporating basic groups like D-ala *S. aureus* that changes the overall charge of surface towards low negative, the increased resistance in *S. aureus* towards AMPs is

due to the occurrence of enzymes which are proteolytic in nature (metalloproteinase-(aureolysin)) and occurrence of active efflux transporters. As in *Salmonella* spp., by altering the lipid A portion and outer membrane protein modulation as in *Yersinia enterocolitica* is also responsible for AMPs resistance [176]. AMPs are proteolytically degraded by *Enterobacteriaceae* so as to exert resistant mechanism, and thereby limit the penetration of AMPs by defending the cell surface of bacteria. The diverse genes in *Enterobacteriaceae*, encoding for AMPs resistance are as PmrAB, PhoPQ, and RcsBCD Phosphorelay system and are signaling pathways. In *Enterobacteriaceae* spp. the release of protease by the OM is the main cause of AMP disintegration. In *P. aeruginosa,* complex formation of AMPs with exopolysaccharides. In *K. pneumoniae*, capsule polysaccharides formation, O-polysaccharide modification in the OM [177] are responsible for the shield formation in the cell surface of bacteria against AMPs. The research has further been augmented in case of AMPs with the widespread of antimicrobial resistance. AMPs are very important with regard to the enhancing the penetration of certain antibiotics [178, 179]. Several drug delivery systems with novelty were executed to deliver AMPs in order to lessen their resistance. List of various antimicrobial peptides from different sources that are under clinical trials presently are mentioned in **Table 1**.

AMPs from humans					
S. no.	**Source**	**Peptide name**	**Amino acid number**	**Anti-bacterial activity**	**References**
1.	Human neutrophils	Cathelicidins	30	F, G−, G+	[180]
2.	Human neutrophils	A Defensins	12-80	F, G−, G+	[181]
3.	*Homo sapiens*	Human Histatin 8	12	F, G−, G+	[182]
4.	Neutrophils (*Homo sapiens*)	LL37	37	F, G−, G+	[183]
From insects					
1.	*Acalolepta luxuriosa*	Acaloleptin	71	G+, G−	[184]
2.	*Drosophila melanogaster*	Andropin	34	G+	[185]
3.	*Apis mellifera*	Apidaecin IA	18	G−	[186]
4.	*Hyalophora cecropia*	Cecropin	37	G−	[187]
5.	*Aedes aegypti*	Defensin-α	40	G+, G−	[188]
6.	*Drosophila melanogaster*	Drosomycin	44	F	[189]
7.	*Holotrichia diomphalia*	Holotricin	43	G+, G−	[190]
8.	*Sarcophaga peregrine*	Sapecin-α	40	G+, G−	[191]
9.	*Tenebrio molitor*	Tenicin 1	43	G+, G−	[192]
10.	*Podisus maculiventris*	Thanatin	21	G+, G−	[193]
From animals					
1.	*Androctonus australis*	Androctonin	25	F, G−, G+	[194]
2.	Bovine Neutrophils	Bactenecin	12	G−, G+	[195]
3.	*Rana brevipora porsa*	Brevinin	24	G−, G+	[196]

AMPs from humans					
S. no.	**Source**	**Peptide name**	**Amino acid number**	**Anti-bacterial activity**	**References**
4.	*Bufo bufo gargarizans*	Buforin II	21	F, G−, G+	[197]
5.	*Cupiennius salei*	Cupiennin	35	G−, G+	[198]
6.	*Phyllomedusa sauvagii*	Dermaseptin S1	34	G−, G+	[199]
7.	*Lycosa carolinensis*	Lycotoxin	27	G−, G+	[200]
8.	*Tachypleus tridentatus* (Horseshoe crab)	Tachyplesins	17	G−	[201]
From microorganims					
1.	*Lactococcus lactis*	Nisin	34	G+	[202]
2.	*Trichoderma viride*	Alamethicin	20	G+	[203]
3.	*Enterococcus*	Enterocin	70	G+, G−	[204]
4.	*Staphylococcus hominis* MBBL 2-9	Hominicin	21	G+, G−	[205]
5.	*Bacillus subtilis*	Ericin S	32	G+	[206]
6.	*Lactobacillus plantarum*	Plantaricin A	26	G+, G−	[207]
7.	*Carnobacterium piscicola*	Carnobacteriocin B2	48	G+, G−	[208]
8.	*Leuconostoc pseudomesenteroides*	Leucocin A	37	G+, G−	[209]
9,	*Bacillus subtilis*	Subtilin	32	G+	[209]
10.	*Pyrularia pubera*	Pyrularia thionin	47	G+, G	[210]
11.	*Escherichia coli* AY25	Microcin J25	21	G−	[211]
12.	*Bacillus brevis*	Gramicidin A	15	G+, G−	[212]
13.	*Pediococcus acidilactici* PAC-1.0	Pediocin PA-1/ AcH	44	G+	[213]
14.	*Leuconostoc mesenteroides*	Mesentericin Y105	37	G+	[214]
15.	*Carnobacterium piscicola* LV17B	Carnobacteriocin BM1	43	G+, G−	[215]
16.	*Bacillus subtilis* A1/3	Streptin 1	23	G+	[216]
17.	*Planomonospora alba*	Planosporicin 24	24	G+, G−	[217]
18.	*Lactobacillus gasseri* LA39	Gassericin A	58	G+, G−	[218]
19.	*Clostridium beijerinckii* ATCC 25752	Circularin A	69	G+, G−	[219]
20.	*Carnobacterium divergens* V41	Divercin V41	43	G+	[220]
21.	*Listeria innocua* 743	Listeriocin 743A	43	G+	[221]
22.	*Lactobacillus plantarum* C19	Plantaricin C19	37	G+	[222]

AMPs from humans					
S. no.	**Source**	**Peptide name**	**Amino acid number**	**Anti-bacterial activity**	**References**
23.	*Enterococcus faecium* P13	Enterocin P	44	G+	[223]
24.	*Bacillus subtilis*	Subtilosin A	35	G+, G−	[224]
25.	*Lactobacillus plantarum* A-1	Plantaricin ASM1	43	G+	[222]
26.	*Bacillus licheniformis*	Lichenin	12	G+, G−	[225]
From plants					
1.	Latex of rubber trees	Hevein	43	F	[226]
2.	Wheat endosperm	Purothionins	45	G+, G−	[227]

F, fungus; G+, Gram-positive; G−, Gram-negative.

Table 1.
List of antimicrobial peptides from different sources that are under clinical trials presently (https://clinicaltrials.gov/, NIH).

7.3 Phage-based therapy

Phage-based therapy, also known as bacteriophage therapy, is an innovative approach to combat antimicrobial resistance (AMR). Bacteriophages are viruses that specifically infect and kill bacteria. They have been recognized as a potential alternative to antibiotics in the battle against bacterial infections, particularly those caused by antibiotic-resistant bacteria [228]. The rise of antimicrobial resistance is a major global health concern, as it reduces the effectiveness of traditional antibiotics, making it challenging to treat certain infections [229]. Bacteriophages, being highly specific to particular bacterial strains, can potentially overcome some of the limitations of broad-spectrum antibiotics and help address AMR in several ways:

Specificity: Phages target specific bacterial species or strains, leaving beneficial bacteria and the human body's microbiota largely unaffected. This specificity reduces the risk of disrupting the natural microbial balance in the body.

Diversity: Phagechigh level of genetic diversity. This diversity means that new phages can be isolated and selected to target emerging antibiotic-resistant strains of bacteria.

Self-replicating: Once a suitable phage is identified, it can replicate within the infected host bacterium, leading to an exponential increase in the number of phages, which can improve treatment efficacy.

Co-evolution: Phages can evolve alongside bacteria, potentially countering bacterial resistance mechanisms through natural selection.

Safety: Phages are generally considered safe for human use, as they are naturally present in the environment and have co-evolved with bacteria.

Biofilm disruption: Phages can penetrate and disrupt bacterial biofilms, which are protective structures that make bacterial infections difficult to treat with conventional antibiotics.

Phage therapy is an evolving field, and its integration into mainstream medical practice requires continued research, investment, and collaboration between

scientists, clinicians, and regulatory bodies. As research progresses, phage-based therapy could become a valuable tool in the fight against antimicrobial resistance and help address the growing global health threat posed by antibiotic-resistant infections.

8. Novel nano formulation approaches for AMPs

Generation, development of new antimicrobials, or AMPs development is considered as a novel way to tackle the emergence and widespread resistance to the known conventional antibiotics by several microorganisms, AMPs were potentially effective in curbing the antimicrobial resistance as compared to the conventional antibiotics. However, AMPs face various problems {e.g., proteolytic degradation, Nonspecific interactions, less stability, selectivity and inadequate *in vivo* activity which render AMPs ineffective to exercise its feat as hampered to arrive at target site}. In order to curtail the problem associated with delivering AMPs alone, attempts are made by researchers for delivering AMPs via developing formulation systems which are novel. AMPs targeting in direct application with alternative ways comes with AMP encapsulation into various nanocarrier. Diverse encapsulated AMPs developed to target AMR includes carbon nanotubes, novel polymeric & lipidic nanoparticles, cubosomes, microspheres, micelles, polymersomes, dendrimers, nanocapsules, and additional colloidal delivery systems. AMPs loaded in nano carriers can assist in combating proteolysis, curbing pitiable bioavailability, or toxicity & susceptibility adhered with AMPs alone. Encapsulated AMPs are delivered to the intracellular pathogens or into the cells which are infected via these nano formulations that act as transporters. Moreover, functional polymer conjugated with AMPs provides new functionalities, improves selectivity by reducing toxicity and acts with potential antimicrobial activity [230]. For the purpose of translating the AMPs and its various formulations from bench to bedside the development of polymer conjugation and novel nano-formulations come up with broad new avenues. While as, very few AMPs and its formulations are actually translated into the clinical trials [231–236].

Besides nanocarriers, researchers also attempted to work on various diverse nanomaterials which are novel showing less susceptibility to develop antibiotic resistance. These novel nanomaterials are structurally nanoengineered antimicrobial peptide polymers (SNAPPs) and star peptide polymers [237]. As proved by *in vitro* and *in vivo* studies, these star-shaped polymers are constructive in microbial carnage, in comparison to the conventional antibiotics, these act through diverse pathways and are less toxic, making them more effective and accepted than the conventional nanocarriers [36].

9. Nanostructured polymeric antimicrobial peptides

Exploiting the line of attack of SNAPPs or polymeric peptides which are nanostructured has revealed efficient activity against both Colistin MDR (CMDR) *A. baumannii* and ESKAPE bugs. Involving the action as: apoptotic cell death pathway initiation, destabilizing outer membrane, and interruption of ionic movement crossways the cell membrane. In the occurrence of SNAPPs prototype (S16) [238] sub-micron levels no wild mutation were observed in *S. aureus* multiplication even after 600 generations, enlightening these SNAPPs hinder resistance.

Commercially developed functional AMPs stereospecific structures are developed by using ROP-NCA (ring-opening polymerization N-carboxy anhydride) technique [239]. In a latest study, ROP-NCA have been utilizing valine (hydrophobic) and lysine (cationic) as amino acid residues, SNAPPs were developed. Likewise, to augment the solubility in water the structures were synthesized with poly(amidoamine) PAMAM dendritic arms using lysine to valine ratio of 2:1 [240]. Elevated Minimum Bactericidal Concentration (MBC) in opposition to *E. coli* has been reported in the structures possessing homolysine residues. In contrast to the host defense peptides which directly circumvent the ESKAPE bugs by bacterial pathway, SNAPPs immunize the mammalian cells against ESKAPE pathogens and CMDR by effecting both bacterial as well as utilizing diverse indirect pathways. By escalating the neutrophil infiltration mechanism the aforesaid indirect pathway is exhibited [35, 241]. Utilization of alpha-amino acids via NCA-ROP techniques are other strategies used to develop AMPs. Even at the lowest MICs against *C. albicans, P. aeruginosa*, *Serratia marcescens*, and MRSA Antimicrobial peptides were found to be highly susceptible consisting of phenylalanine, lysine in the ratio of 15:10 and lysine (hydrophilic moiety), leucine and phenylalanine as the hydrophobic moiety in the ratio of 10:7.5:7.5 [242–244]. Owing to the nanostructures, localization of the charges increases efficacy of the AMPs by bacterially induced peptide aggregation, which are formulated as SNAPPs. Polymers which are cationic in nature are chosen as with bacterial surface they exhibit electrostatic interactions. Protonated polyesters, polyethyleneimines, polyarylamides, and polymethacrylates are examples of few cationic polymers which are synthesized. By changing the length of carbon chain of the functionalities side group for the development of various polypeptide libraries gave comprehensive idea that these are potentially efficient against a broad spectrum of Gram-negative and Gram-positive bacteria and also curtail the formation of Biofilm particularly against *E. coli* and *S. aureus* [245, 246].

10. A ray of hope-star polymers

Using diverse polymeric structures in the approach of novel delivery system which evolved extremely with the purpose to improve the biocompatibility, stability, and therapeutic efficacy of the antibiotics. With the purpose to improve antibiotic delivery the various noteworthy approaches undertaken are as nanoparticles, polymeric carriers which are hydrophobic and hydrophilic, and targeting moieties, towards antibacterial therapy from gene delivery, In the field of biomedical applications, star polymers has achieved significance for novel delivery system. Star polymers consist of arms which are linear (contrasting dendrimers with branched arms) and form simpler structures and characteristics such as biocompatibility, simpler structure (lower viscosity solution), and introduction of functional groups are gaining attention in the biomedical research field. In order to execute cell-specific targeting, star polymers with multifunctional central part having at least three macromolecular chain can fasten to a targeting moiety [247, 248]. With the widespread emergence of AMR (ESKAPE bugs), this strategy gained focus wherein linear start polymers are integrated with an antibiotic and has resulted in the improvement of antimicrobial therapy. Which includes attachment of antibacterial groups or AMPs that are polycationic (e.g., poly(2-dimethylaminoethyl methacrylate), star polymers which are poly(2-(dimethylamino) ethyl methacrylate) PDMAEMA based are susceptible to *E. coli* (MIC < 250 μg/ml, 99% in 2 h) [247, 248]. Studies relevance with regard to

the inclusion of AMPs inside these star polymers has demonstrated augmenting of improved encapsulation characteristics via this process and star polymer's compartmentalized functionalities that gave rise to the idea of functionalized stars with stereospecificity. Ring-opening polymerization technique is adopted for the generation of these polymers which are star-shaped. Core-cross linked stars (CCS) also referred as Stereospecific stars, were synthesized by ring-opening polymerization technique of amino acid poly (ε-Z-L-lysine) N-carboxy anhydride (NCA), which serves as the macromolecular initiator or arm, following by the adding of the L-cystine (agent poly cross-linking). Water solubility of the CCS is enhanced by the deprotection of the arms, additionally improved the biocompatibility of star polymers [246, 249–251].

11. Caragenins

"Caragenins", a new-fangled adjuvant class, developed so as to surmount the aforesaid concerns associated with the AMPs usage; these are cationic steroidal antibiotics (CSA), in which an aminoalkyl function substitutes the sterol core structure's alkoxy groups. This substitution in the structure makes "Caragenins" resistant to the proteases because they can be produced in larger amounts as their structure is devoid of peptidic bonds. Furthermore, CSA are able to complex with phospholipids and are capable to stably get incorporated into the membranes [252, 253]. CSA are positively charged and interact to the negatively charged membranes (protozoa, bacteria, fungi, and viruses) via electrostatic force of attraction and through the disruption of the membrane leading to cell death [254, 255]. Synthesis of caragenins such as CSA-8 and CSA-13 was in a way so that they imitate the physico-chemical properties of cationic structural of AMPs, with a comparable mode of action, that is based on (i) stimulation of bacterial membrane swift depolarization and (ii) improved permeabilization in the outer membrane of Gram-negative bacteria. In a specific order so that CSA-8 and CSA-13 make bacteria more prone to susceptibility towards antibiotics (e.g., erythromycin antibiotic when used alone against *K. pneumoniae* resistant strain the MIC is reported as 70 μg/ml, but the combination of erythromycin with CSA-8 compounds decreases the MIC value to 1 μg/ml. Anti-microbial activity of CSA-13 was analyzed on carbepenem resistant strains. It has also been reported that the combination of CSA-13 with antimicrobials, the synergy was attained with tobramycin-35% and colistin-55%, on the contrary there was no observation of antagonism [253, 256]. Wide-ranging research is required for the development of this type of antibiotic adjuvant class with an aim to enhance the absorption, distribution, metabolism, and excretion (ADME) profile of these molecules, in order to allow them to enter clinical trials and finally make entry into market.

12. Conclusion

Antimicrobial resistance poses a widespread threat to patients, health care systems and overall global economy. Using diverse mechanisms of action bacteria develop resistance and multi-drug resistance (MDR) is now the rule rather than the exception. The key driver for the emergence of resistance is the extensive use of antibiotics. A major concern with regard to the control of infectious disease is the dearth of the antimicrobial agents. ESKAPE bugs are becoming self-reliant as they are destroying antimicrobial delivery stratagem. Several drug delivery systems that are novel

and copy the peptides natural bacteriolytic action have been reported involving Antimicrobial peptides, via incorporation of these peptides into nano-carriers and into star-shaped polymers. The ultimate structure and architecture of the star polymers is well described by the SNAPPs that show supplementary apoptotic mechanism switched as they make entrance into the bacteria and therefore, show promising future in curtailing AMR. Using ROP technique, AMPs synthesis techniques are in confines. Nevertheless, widespread research is required for AMPs synthesis so as to yield reproducible and cost-effective outcomes. The future ambition for the upcoming research to verify a series of therapeutic activities will be the modulation of the functionalities on the star polymers surface. Moreover, the production and the antimicrobials use are perplexed with a very complex network of stakeholder interests that extends well beyond the boundaries of medicine. Specifically, the immense majority of antimicrobials are fed to animals and, in various countries, the antimicrobials therapeutic in humans is regulated poorly. This imposes a colossal selection pressure on microbiota in various ecosystems that will unavoidably result in a few bacterial genotypes competent of surviving. The antimicrobial resistance mechanism of defense have been chosen during evolution can readily be dispersed into other ecological compartments, including pathogens, by sophisticated HGT mechanisms. Therefore, the problem of antimicrobial resistance cannot be dealt simply by the introduction of new antimicrobials. It requires the combined efforts of governmental organizations, regulatory agencies, health-care professionals, veterinarians, agricultural specialists, educators, researchers, and stakeholders to retain the therapeutic benefit of antimicrobials for efficient control of infectious diseases. In order to combat the widespread it will require the multidisciplinary efforts so as to limit the extensive antibiotic use and to implement avoidance and control measures to limit transmission of these dangerous pathogens.

Conflict of interest

The author(s) declare that there are no conflicts of interest.

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