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Review

Review of new insights into antimicrobial agents

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Abstract: People have known the bacteria and have used various ways to deal with them, from a long time ago. Perhaps, natural antibiotics with have been the first step in fighting against pathogens. However, several factors, such as dealing with unfamiliar bacteria or emergence of drug-resistant species, have motivated us to discover new antibiotics or even change previous types. In this regard, a variety of natural and synthetic antibiotics with different origins, mechanism of action, structures and functional spectrum, have been developed and used. Some impact on the synthesis of nucleic acids and some affect protein synthesis so destroy bacteria. There is a ring in the structure of most of the antibiotics which gives them special properties. However, despite their numerous advantages, antibiotics also have drawbacks ehich limit their use in all situations. Therefore, other approaches such as photodynamic therapy (PDT) and antibacterial peptides were considered as alternatives. Photodynamic therapy (PDT) is a treatment that uses photosensitizing agents, along with light, to kill bacteria. The photosensitizing agents only work after they have been activated by certain kinds of light. Antibacterial peptides are a unique and diverse group of molecules which have between 12 and 50 amino acids in general. In this paper, will reviewt hree mentioned topics, namely antibiotics, photodynamic therapy and antibacterial peptides and will discuss the advantages and disadvantages of each approach briefly.

Key words: Antibiotics; Photodynamic therapy (PDT); Antimicrobial peptides.

Introduction

Antimicrobial agents have been used for more than 2000 years. There are evidences that ancient Egyptians and Greeks used special molds and plant extracts to control infections. Although, it was not until the later half of the 19th century that microorganisms were found to be responsible for a variety of infectious diseases (1).

Beside antibiotics, Photodynamic therapy (PDT), which was approved by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions of the face or scalp (2) has emerged in recent years as a non – invasive therapeutic approach for the treatment of various infections (3).

Photodynamic therapy (PDT) is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light (4). Each photosensitizer is activated by light of a specific wavelength and produce a form of cytotoxic reactive oxygen that kills nearby cells (5). Antimicrobial PDT can easily provide the access to the whole dental root surface and its application in the treatment of periodontal diseases has been studied extensively (6). Also, PDT can inactivate endotoxins such as lipopolysaccharide by decreasing their biological activity (7).

Antimicrobial peptides (AMPs) are some kinds of oligopeptides containing a few to several hundred amino acid residues and have been used against a variety of microorganisms such as viruses, bacteria and parasites (8). Defensin is the most famous Antimicrobial peptides until now. It is believed that in animals, AMPs are the first line of defense against foreign pathogens (9). Overall, more than 5,000 AMPs are known so far of natural or synthetic origins (10). In following chapter, we discuss about these principle antimicrobial agents with more details.

Antibiotics

The first antimicrobial agent, salvarsan, was synthesized by Ehrlich in 1910 to eradicate syphilis (11). In 1928, Fleming found that penicillium fungi would produce substances that could inhibit the growth of Staphylococcus aureus in culture dishes. The compound was named penicillin and came into clinical use in the 1940s (12). In 1935, Domagk developed sulfonamides, the synthetic compounds with a broad limitation range in terms of safety and efficacy (13). In 1940s, streptomycin, an aminoglycoside antibiotic, and thereafter, chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g., vancomycin) were discovered from soil bacteria (14). Following this trend, the quinolone antimicrobial agent, nalidixic acid, was synthesized in 1962 (15). After that, β-lactam antibiotics, a broad class of antibiotics, consisting of all antibiotic agents that contain a β-lactam ring in their molecular structures, were developed and introduced to the pharmaceutical market. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems (16). Cephems, including cephalosporins and cephamycins, were developed in the 1960s and bases on their antimicrobial spectra, they are classified several generations (17). Later, Carbapenems were developed as a group of strong effective drugs not only for Gram-positive and Gram-negative bacte-

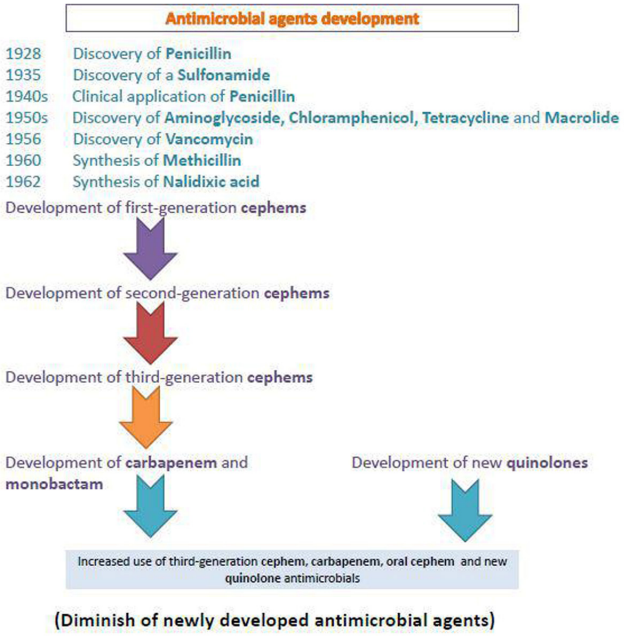

Figure 1. Historical trajectory of antibiotics development.

ria but also anaerobes (18). Following the progress of development of new antimicrobials, Nalidixic acid, as the first quinolone antimicrobial, was developed to target Gram-negative bacteria specifically with poor tissue distribution (19). Entering quinolones antimicrobial drugs to market promised the fact that it goes towards developing more specific drugs with fewer side effects. Trend of development of antibiotics is schematically illustrated in Figure 1.

Proper and successful antibiotic characteristics

An antibiotic treatment can be considered successful if the antibiotic agent, like other drugs, has some traits such as (20):

I. It should not have any side effect or its side effect should be slight. On the other hand, it must have selected toxicity.
II. It should have a broad spectrum effectiveness and can eliminate different bacteria.
III. It should have proper bioavailability and pharmacokinetics.
IV. It should be stable enough without loss or change of properties.
V. It should have an appropriate clearance rate.
VI. It should be cost-effective and available.

Antibiotic classification

Antibiotics can be classified based on their origin, mechanism of action, chemical structure and activity spectrum.

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Origin Classification

Bacteria, fungi, plant are able to produce antibiotics. Some species of genus bacteria produce secondary metabolites with diverse chemical structure. For example, a number of antibiotics are produced by different bacillus spp (21). Most classes of antibiotics derived from natural sources, are assorted as Beta-lactam antibiotics, tetracyclines, aminoglycosides and macrolides. On the other side, synthetic antibiotics include sulfa antibiotics, quinolones and oxazolidinones. Many bacterial origin antibiotics inhibit the growth of another bacteria (22).

Mechanism of action classification

Inhibition of DNA replication

The quinolones (comprising nalidixic acid and ciprofloxacin) target DNA gyrase (topoisomerase II) and topoisomerase IV (topoIV). They actually trap these enzymes at the DNA cleavage stage and prevent strands from joining again(23). The susceptibility of these targets to quinolones, varies among bacterial species; while topoIV is the primary target of quinolones in gram-positives, DNA gyrase is the primary target and topoIV the secondary target of these drugs in gram-negative bacteria (23). Therefore, the net effect of quinolone treatment is to generate double stranded DNA breaks that are trapped by covalently linked topoisomerases (24). Furthermore, induction of SOS proteins expression following by DNA damages, could be another advantage that enhances the efficiency of this class of antibiotics.

Inhibition of RNA synthesis

Rifamycin category drugs, are a broad category of semi-synthetic antibiotics. They isolated from the Gram-positive bacterium, Amycolatopsis mediterranei (originally Streptomyces mediterranei) for the first time(25). Rifamycins bind to the prokaryotic RNA-polymerase enzyme with high affinity and inhibit DNA dependent transcription. The main target area of these drugs, is the subunit located within the channel formed by the polymerase-DNA complex, from which the newly synthesized RNA strand emerges (26). In fact, the nascent RNA strand initialization stage is inhibited by Rifamycins (27).

Inhibition of cell wall synthesis

β-lactams and glycopeptides interfere with specific steps in homeostatic cell wall biosynthesis. Successful treatment with a cell wall synthesis and induce cellular stress responses by changing cell shape and size (28). The goal is achieved by inhibiting the peptide bond formation reaction which is catalyzed by transpeptidases and transglycosylase or through binding with PG units (at the D-alanyl-D-alanine dipeptide) and also blocking the activity (29, 30). It is worth noting that β-lactams are effective in treatment of Gram-positive and Gram-negative infections, whereas glycopeptides are effective only against Gram-positive bacteria due to their low permeability. Antibiotics like Fosfomycin and Bacitracin, inhibit the cell wall synthesis by blocking transport of individual PG units. Lipopeptides like Daptomycin, affect structural integrity via their ability to insert into the cell membrane and induce depolarization (31). All mechanisms that have been discussed here, are involved in a process called 'lytic cell death' in which, overgrowth of cell wall leads to increased pressure inside the cell and its bursting (32). However, it must be noted that the lysis-dependent cell death mechanism is much more complex, involving many active cellular processes (33). In addition to lytic cell death, evidences suggest that there are some non-lytic pathways regulated by bacterial two-component systems (34). For example, the LytSR two-component system can affect cell lysis by regulating autolysin activity in Sta-

phylococcus aureus (35). So, until now it has become clear that antibiotics can destroy the cell wall of bacteria through lytic, non-lytic or both processes. But another mechanism by which some antibiotics result in the destruction of the bacterial cell, is induction of SOS response. For instance, β-lactams that inhibit Penicillin binding protein 3 (PBP-3), induce filamentation and stimulate the DpiAB two-component system, which can activate the SOS response (36). On the other hand, DNA damaging antimicrobiotics, such as quinolones, may cause filamentation through induction of the SOS response (37).

Inhibition of protein synthesis

Macrolides (e.g., erythromycin), lincosamides (e.g., clindamycin), streptogramins (e.g., dalfopristin/quinupristin), amphenicols (e.g., chloramphenicol) and oxazolidinones (e.g., linezolid) inhibit 50S compartment of ribosome (38). Actually, they block either initiation of protein translation (39) or peptidyl-tRNAs translocation, which serves to inhibit the peptidyltransferase reaction that elongates the nascent peptide chain. Several models are proposed to explain the mechanism by which these antimicrobial classes act; including inhibition the access of peptidyl-tRNAs to the ribosome, blocking the peptidyltransferase elongation reaction by steric inhibition, and dissociation of the peptidyl-tRNA (40). Also, it is demonstrated that these classes of antibiotics lose their activity when elongation has progressed beyond a critical length (41). Tetracyclines and aminocyclitols are accounted as 30S ribosome inhibitors by blocking the access of aminoacyl-tRNAs to the ribosome (42) and binding to the 16S rRNA component, respectively (43). Spectinomycins, inhibit elongation factor-catalyzed translocation (44), while aminoglycosides interact with 16S rRNA compartment hence induce conformational alternation of the mRNA-codon complex and its cognate charged aminoacyl-tRNA at the ribosome. It leasds to tRNA mismatch promotion that could be followed by protein mistranslation (45). Macrolides, streptogramins, spectinomycin, tetracyclines and chloramphenicol are typically used as ribosome inhibitors, but behave in a species-specific or treatment-specific fashion (46). This must be related to the sequence differences of the highly conserved ribosomal proteins and RNAs in the variable regions among bacterial species (47). The action mechanism of different types of antibiotics is shown in Figure 2.

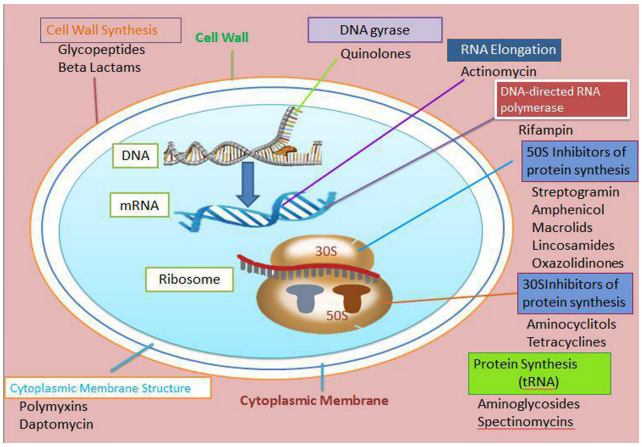

Figure 2. The mechanism of action of different types of antibiotics. Antibacterial action generally falls within one out of four mechanisms, three of which involve the inhibition or regulation of enzymes involved in cell wall biosynthesis, nucleic acid metabolism and repair, or protein synthesis, respectively. The fourth mechanism involves the disruption of membrane structure. Many of these cellular functions targeted by antibiotics are most active in multiplying cells.

Chemical structure classification

Beta-lactams

Beta-lactams including a beta-lactam 'ring' that binds to the active site of the bacterial enzymes. This antibiotic contains sub classes included penicillins, cephalosporins, monobactams, carbapenems (48).

Penicillins are constructed by penicillium notatum. Beta-lactam ring in this sub class, includes a nucleus of 6-aminopenicillanic acid (49).

Cephalosporins are produced by cephalosporium acremonium. Beta-lactam ring includes 7-aminocephalosporanic acid nucleus and side chain has 3, 6-dihydro-2H-1, 3-thiazine rings (50).

Monobactams are made by chromobacterium violaceum. This antibiotic just owns Beta-lactam ring (51).

Streptomyces cattleya is the natural origin of. carbapenems The chemical structure of this sub class is similar to the penicillins (52).

Macrolides

A chemical substance constructed by saccharopolyspora erythraea is macrolides. They are antibiotics with a lacton ring contains 14-16 atoms in their molecule. Macrolides are divided as Erythromycin, Clarithromycin, oleandomycin and Azithromycin. In azalides (azithromycin) the atom of nitrogen is present in a cycle (53).

Tetracyclines

Tetracyclines are produced by various Streptomyces species. The chemical structure of tetracyclines, comprises 4 hydrocarbon ring. These antibiotics act as an inhibitor of protein synthesis in bacteria need the amino group in position C4 and keto-enolic tatuttomers in position C1 and C3 of the A ring. The amino group in the C4 position is pivotal for the antibacterial activities. These antibiotics have partially hydrated nucleus of tetracene. Tetracyclines are classifies as first generation, second generation and third generation (54).

Aminoglycosides

These antibiotics have the cyclohexan structure with OH- and NH2-, or guanidino-derivatives and glycoside derivatives with one or certain OH- groups. Some derived from Streptomyces genus or Micromonospora. Example of these antibiotics are streptomycin, kanamycin, gentamicin and neomycin (55).

Glycopeptides

Glycopeptides are glycosylated cyclic or polycyclic non-ribosomal peptides produced by groups of filamentous actinomycetes. These therapeutics target gram positive bacteria by binding to the acyl-D-Ala-D-Ala terminus to the growing peptidoglycan and then cross-linking peptides within and between peptidoglycan on the outer surface of the cytoplasmic membrane (56).

Polyenes

Polyenes have differences in the number of conjugated

carbon-to-carbon double bonds in their molecule, the size of the conjugated ring and the presence or absence of a hexosamine sugar or aromatic moiety in the molecule (57).

Activity spectrum classification

Depending on the range of susceptible bacterial species, antibiotics are classified as broad-spectrum, intermediate-spectrum, or narrow- spectrum (58). Note that the spectra of activity may change with acquisition of resistance genes, as will be discussed in the next module.

Broad spectrum antibiotics are active against both gram-positive and gram-negative microorganisms.

Narrow spectrum antibiotics have limited activity and are only useful against particular species of microorganisms primarily.

Penicillins are one of the antibacterials that kill bacteria by inhibiting formation of the bacterial cell wall. These antibacterials are effective in treatment of disease in poultry (49). Cephalosporins are beta lactams antibiotics and structurally are similar to penicillins. This antibacterial complex with bacteria cell walls and disrupt the synthesis of the peptidoglycan. Cephalosporins are divided into first, second, third, fourth and fifth generations. Each generation has a broader spectrum of activity than the one before. Cephalosporins include cefazolin (1st generation), cefoxitin (2nd generation), ceftriaxone (3rd generation), cefepime (4th generation) and ceftaroline (5th generation) (53). Aminoglycosides are produced by several species of Streptomyces. This agent blocks synthesis of essential protein for growth of the bacteria and used for treatment of anaerobic gram negative bacilli infections. They are useful for treatment staphylococcal and enterococcal infections as well. Example of aminoglycosides are streptomycin, gentamicin, spectinomycin, neomycin and kanamycin (53). Glycopeptides inhibit bacterial cell wall peptidoglycan synthesis. These antibiotics are effectives against gram positive cocci including S.aureus and S.epidermidis. Teicoplanin and vancomycin are two instances of glycopeptides (3-5). Tetracyclines are one of the broad spectrum antibiotics that are effective for treatment of intestinal infections and chlamydial infections (53).

Carbapenems have the broadest spectrum among all beta-lactams. This antibiotic binds to the PBPs just like cephalosporin and penicillin thus preventing the bacterial cell wall synthesis. Carbapenems are effective against many gram-positive bacteria and gram negative bacteria (59).

Activity spectrum of Oxazolidinones encircles gram-positive bacteria (MRSA, penicillin resistant streptococci, VRE) .This antibacterial can bind to 50S subunit of ribosome and prevent protein synthesis (60). Polymixins have cyclic peptide with a long hydrophobic chain. They attach to phospholipids of bacteria and disrupt cell membrane. These antibiotics are produced using non-ribosomal peptide synthetase systems in gram-positive bacteria (60). Quinolones are one of the antimicrobials that are effective for treatment of intestinal infections. Quinolones inhibit of DNA replication. These antibiotics have been classified in four generations based on their activity spectrum (60).

Photodynamic therapy (PDT)

Antimicrobial photodynamic therapy (PDT) represents an effective alternative method to inactivate bacteria, fungi, viruses and protozoa (61). PDT is applied through irradiation of the light to an infected tissue that has been exposed to a photo-sensitive dye (PS) which is often derived from pigments such as heme, chlorophyll and bacteriochlorophyll containing tetrapyrrole aromatic nucleus (62). The PS should have relatively high absorption bands (>20,000–200,000 M−1cm−1), a high yield of excited electronic triplet state, singlet oxygen and low levels of dark toxicity (62). Following the excitation of the PS by visible light into the long-lived triplet state, ROS will be generated through two mechanisms. In type I mechanism, this particular state of the PS interacts with molecular oxygen by electron transfer and forms superoxide anions that may lead to produce more reactive species such as hydroxyl radicals. While in type II mechanism, the PS interacts with molecular oxygen by energy transfer following by singlet oxygen production (63). So, both processes irreversibly alter vital components of cells resulting lethal damage. Mechanism of action of photodynamic therapy is schematically illustrated in Figure 3.

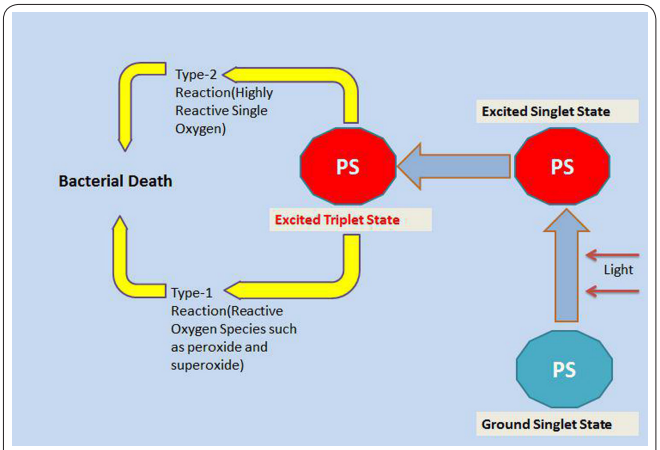

Figure 3. Mechanism of action of photodynamic therapy. When a photosensitizer (PS) is in its excited state, it can interact with molecular triplet oxygen and produce radicals and reactive oxygen species (ROS) and highly reactive single oxygen. These species can interact with cellular components including unsaturated lipids, amino acid residues and nucleic acids and result in target-cell death (only within the illuminated area).

Of course, this point should kept in mind that PS should selectively be uptaken by bacterial cells and does not operate in the dark (64). PTD mainly damage cell membrane and DNA. Damage to the plasma membrane usually is followed by uncontrolled release of metabolites into and out of the cells and damage to DNA is usually irreversible (65). Some common photosensitizers display anti-microbial photocydal action are listed in Table 1.

The use of PDT to eliminate gram-positive bacteria is fairly easy, because their cell wall is a porous layer. However, due to the existence of an outer wall with a low permeability, elimination of Gram-negative bacteria is a bit more complicated (66). To overcome this difficulty in Gram-negative bacteria, methods such as the use of outer membrane disorganizing agents, photosensitizers with cationic charges and optimization of the chemical structure of PS are proposed (67). Generally, the main advantages of PDT are its specificity, limited side effects, the prevention of infection recurrence and the lack of development of multidrug resistant microorganisms (68). PTD method has been used to eliminate a variety of bacteria such as periodontopathogenic bacterial species (Porphyromonas gingivalis, Fusobac-

Table 1. Common photosensitizers displaying anti-microbial photocydal action with their origins.

Class of compounds	Name	Site of action in prokaryotic cells
Natural products	Furanocoumarin	DNA intercalation
	Perylenequinonoin hypericin	Inhibitor of protein kinase C
Phenothiazines	Methylene blue	DNA interaction
	Toluidine blue	Plasma membrane
	Acridine	DNA interaction
Cyclic tetrapyrroles	Phthalocyanine porphyrine	Membrane/cytosolic sites

terium nucleatum, and Capnocytophaga gingivalis) (69), endodontic pathogens (Enterococcus faecalis) (70), Propionibacterium acnes (71), Proteus mirabilis and Pseudomonas aeruginosa (72).

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are a group of oligopeptides containing a few to several hundred amino acid residues and have been used against a variety of microorganisms such as viruses, bacteria and parasites (8). The first recognized antimicrobial peptide was extracted from soil Bacillus bacteria in 1939 by Dubos and Hotchkiss. They found that the extract can protect mice against pneumococcal infections and after closer investigation, it was discovered that active component of the extract is a peptide and named that gramicidin (73). Tyrocidine, another AMP, was discovered in 1941 and found to be detrimental against gram-positive and gram-negative bacteria (74). However, after a while it turned out that tyrocodine is toxic for human blood cells (75). In the same year, another AMP ,which later named purothionin, was extracted from the plant Triticum aestivum and its damaging effects against fungi and bacteria were proved (76). In later years, AMPs were also extracted from animal sources; for example, defensin was isolated from rabbit leukocytes (77), bombinin from epithelia (78), and lactoferrin from cow milk (79). It is believed that AMPs are the first line of defense against foreign pathogens in animals (9). In addition, it was demonstrated that the human leukocyte lysosomes also contain AMPs (80). Overall, more than 5,000 AMPs are known so far with natural or synthetic origins (10). Some AMPs genes expression is in housekeeping manner, while for others, the gene expression is inducible. For instance, Wang and colleagues demonstrated that the rate of defensin mRNA transcription in rat will be increased following by infection with Pseudomonas aeruginosa (81).

It's also known that AMPs are involved in regulation of inflammatory responses in the host during infections. For example, it is found that bacterial lipopolysaccharides can induce the production of AMPs in mammals which, in turn, can modulate the inflammatory response. (82). In contrast, antibiotics may cause severe inflammatory reactions due to lack of immunomodulatory capability (83). It should be noted that the production of AMPs in eukaryotic cells such as lymphocytes (9), phagocytes (84) and epithelial cells (85) has been demonstrated.

Structure of AMPs

According to the conducted studies so far, AMPs structures are as β-sheet, α-helix, loop and extended form from which, α-helix is the most common structure (86). AMPs like magainin, protegrin and coiled indolicin have α-helix structures (87). It should be noted that the structure of many AMPs change based on environmental conditions. For example, indolicin has a globular structure in hydrophilic environment and is wedge-shaped in hydrophobic conditions (88).

Mechanism of action

AMPs specifically target bacterial lipopolysaccharide layer and unlike antibiotics, have fewer side effects for eukaryotic cells (89). In addition, AMPs exert their killing effect much faster than antibiotics and can also increase the effect of antibiotics in a synergic manner. For instance, the combination of ampicillin with nisin Z kill Pseudomonas fluorescens with 155-fold lower minimum inhibitory concentration (MIC) (90). Other advantages of AMPs compared to antibiotics are the possibility of chemical synthesis and easily changing the structure to modify their functions (91).

AMPs (cationic AMPs) that target bacterial cell membranes, degenerate the lipid bilayer structure (92) and finally kill bacteria by inhibiting DNA replication and protein synthesis (93). Most AMPs are amphipathic, which means that they have both hydrophilic and hydrophobic faces. This feature gives them the ability to penetrate the cell membrane (94). Also, some of them could create holes in the cell membrane and facilitate the entrance of others (Figure 4).

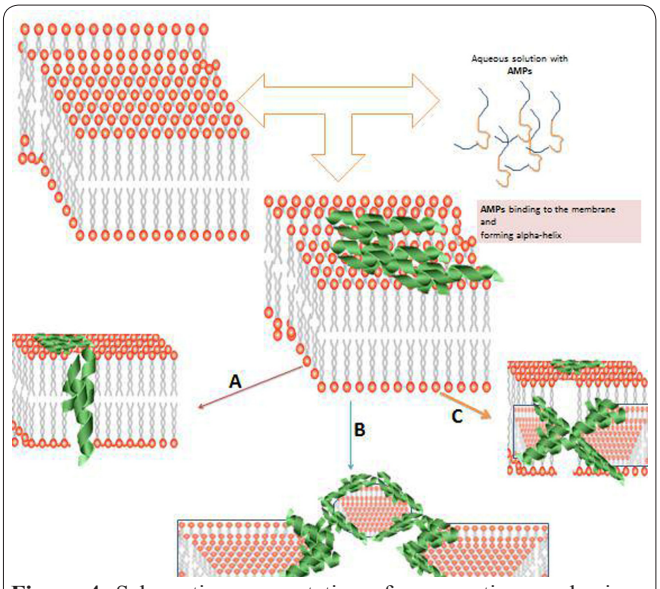

Figure 4. Schematic representation of some action mechanisms of AMPs. (A) Due to the amphipathic structure, AMPs penetrate into the cell perpendicularly. (B) Carpet model. AMPs molecules coat the membrane as their hydrophobic part faces external creating pores in the membrane. (C) Toroidal pore model. In this model, several AMP molecules form the barrel-shaped structure, So that the hydrophobic parts placed outside and the hydrophilic sides placed inside the barrel.

Table 2. Antimicrobial peptides structures and the relationship between peptide structure and antibacterial activity.

AMP Structure	Example	Activity Type	Disruption Model
Alpha- helices' peptides	Cecropin	Most alpha-helical AMPs disrupt bacterial membranes by forming	Carpet
	Magainin	amphipathic helix in membranes	Barrel slave
Beta-sheet peptides	Pexiganan	Many AMPs with beta-sheet structure exert antimicrobial activity by	Toroidal
	Alpha-Defensins	disrupting bacterial membranes	Toroidal
Extended peptides	Protegrin	Most extended AMPs are not active against membrane of pathogens and	Interaction with intracellular proteins[b]
	Indolicidin	penetrating across membranes	
	Beta-Defensins		
Loop peptides	Bac7	Disrupting bacterial membranes	-
	Bac5		
	Lactoferricin B		
	Thanatin		
	Bactenecin-1		

Some AMPs are able to kill antibiotic resistant bacteria (95). Antimicrobial peptides have mitogens properties. These properties including ability to stimulated growth of fibroblast and epithelial cells in vitro for antimicrobial activity and preventing microbial infection (96). The main antimicrobial structures along with their functions are shown in Table 2.

The resistance strategies of microorganisms to Antimicrobial peptides (AMPs)

It is not unbelievable that bacteria utilize various resistance strategies to avoid antimicrobial peptide (97). Some microorganisms change their net surface charges. For instance, *Staphylococcus aureus* transports D-alanine from the cytoplasm to its teichoic acid it means the negative charge is declined by amine groups (98).This bacterium can also modify its anionic membranes via MprF with L-lysine and make it positive (98). Klebsiella pneumonia polysaccharide capsule can hinder the interaction of these peptides with membrane (99). Salmonella species benefit from another survive strategy. They add myristate to Lipid A with 2-hydroxymyristate that ends to hepta-acylated Lipid A formation by adding palmitate. In this regard, their outer membrane fluidity decreases due to hydrophobic interaction. This interaction can repulse AMPs insertion and pore formation.

A number of gram-negative bacteria, change in their outer membrane proteins (100). Non-typeable Hemophilus influenzae carry AMPs inside the cell and deteriorate them. H. influenzae convert its membrane in a way that seems to be under attack of AMPs. (101). Other strategies are ATP-binding cassette transporters and the resistance-nodulation cell-division efflux pump which carry out these peptides (102); which are fundamental tools for AMPs resistance. Bacterial proteases can also be beneficial way to eliminate AMPs (103). Gram-negative bacteria can produce outer membrane vesicles which attach to peptides and push them away (104). These vesicles also contain lytic enzymes as proteases and peptidases that can act on extracellular. Cyclic-di-GMP signaling had also been developed in the regulation of *Pseudomonas aeruginosa* resistance to AMPs (105).

Whereas they are variety natural ways of resistance, worries are raised due to the fact that Amps resistance can happen at faster rates than before. It means we should be concerned about their clinical use and also physiological functions. (106). Further researches are essential to decide whether it is worth it or not.

Conclusion and future perspective

The combat with different kinds of microbial infections alike bacterial, fungal etc., constitutes a huge challenge for medical sciences. The scope and number of anti-microbial agents with different mechanisms is too much but a few of these technics have been executable in medicine until now. So, more studies are required to attain more effective and executable agents. Here, we elaborated on the three famous and applicable anti-microbial mechanisms and described their details.

For many years, people have knon bacteria as pathogens and have adopted various ways to deal with them (107) Studies have shown that the use of antibiotics dates back to ancient times. For example, human skeletal remains from ancient Sudanese Nubia dating back to 350–550 CE was found with some traces of Tetracyclines (108). However, several factors have encouraged the development of antibiotics and among them, is the emergence of resistant strains to antibiotics. So, there has to be a constant regeneration of new antibiotics to go after these progressively more resistant bacteria. Today, different antibiotics are in use based on origin, mechanism of action, structure and activity spectrum. Although most antibiotics are extracted from natural origins, some are synthetic or produced by changing natural antibiotics (109). Three basic mechanisms of antibiotic action against bacterial cells are inhibition of cell wall synthesis, inhibition of nucleic acids synthesis and inhibition of protein synthesis (31). Based on their chemical structure, antibiotic are categorized as several classes including β-lactams, Macrolides, Tetracyclines, Aminoglycosides, Glycopeptides and Polyenes (110). Also, based on their activity spectrum, some antibiotics kill Gram-negative bacteria, some deteriorate gram-positive bacteria, and some

kill both (111). In addition to antibiotics, other approaches have been developed and used to eliminate bacteria. Photodynamic therapy or PDT utilizes photosensitizing agents, oxygen and light, to create a photochemical reaction that selectively destroys target cells. Photosensitizing agents are drugs that are administered into the body through topical, oral or intravenous routs. In the body, they concentrate in target cells and only become active when light of a certain wavelength is directed onto the area where the target is. The photodynamic reaction between the photosensitizing agent, light and oxygen kills the target cells (112). Antimicrobial peptides (AMPs) are oligopeptides with five to over a hundred of amino acid residues. AMPs target a broad spectrum of organisms. Historically, they were also known as host defense system's cationic, anionic or amphipathic molecules.

The better understanding of these anti-microbial mechanisms opens up new avenues for progress towards a new invention in targeting infections.

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