BAOJ Microbiology

Shimon S, BAOJ Microbiology 2019, 5: 3
5: 050

Review

The Quest for Selective Antimicrobial Agents
The Antimicrobial Peptides and Their Surrogates Approach

Shimon Shatzmiller*

Department of chemical sciences, Ariel University, Ariel, Israel

Recently, the microbiome has attracted the focus of research since it is believed that this companion and nemesis has a crucial influence on our health and behavior, diet and aging. To influence the constitution of this blend of microbes to present differently in the various sections of our body may be the determining factor to work together with this microbial word to bring remedy to many diseases that are considered nowadays incurable [1,2]. Antimicrobial host protection peptides are produced by all complex organisms as well as some bacteria and have a wide range of antimicrobial activities. Collectively, these peptides demonstrate a wide range of antibacterial and antibacterial activities and methods of action; one should distinguish between direct bacterial actions and indirect actions against these pathogens. The structural requirements of peptides for anti-viral activity and anti-bacterial activity are assessed in view of the primary and secondary structures found for host protection peptides. Peptides with antifungal and antiparasitic activity are discussed in less detail, although the full spectrum activity of such peptides indicates that they are essential to host protection molecules. Knowledge about the relationship between peptide structure and function as well as their mechanism of action is applied in the design of antimicrobial peptide variants as potential innovative treatment agents [3,4]. Antimicrobial peptides (AMPs) have recently attracted considerable attention as promising antibiotic candidates, but some obstacles such as toxicity and high synthesis must be addressed before they are developed. For short peptide development with improved cell selectivity, we designed a series of different PMAP-36 analogs. Antimicrobial assays have shown that a chain length reduction in a particular range has maintained the high antimicrobial activity of the peptide and reduced hemolysis parents. The 18MI RI18 peptide showed excellent antimicrobial activity against bacteria and fungi, and its hemolytic activity was lower than PMAP-36 and melittin. The selective indices of RI18 against bacteria and fungi improved by 19 and 108 times, respectively, compared to PMAP-36. In addition, serum did not affect RI18 antibacterial activity against E. coli, but inhibited antifungal efficacy against C. albicans. Flow cytometry Observation electron microscopy revealed that RI18 killed microbial cells primarily by damaging the integrity of the membrane [5], leading to the complete cell lysis. Together, these results show that RI18 has the potential for further therapeutic research against bacteria and fungi that often arise. Meanwhile, the modification of AMPs is a promising strategy for novel microbial development to overcome drug resistance [6]. The technology described here is based on the defense mechanisms of nature. The membranes of microbial cells are destroyed. This unique technology is a new type of microbial treatment that activates the living microbes themselves and processes for its elimination. It based on natural products, anti-microbial peptides that are the basis for innate immune systems of all living organisms on the planet. These compounds were considered a potential treatment due to their activity in the broad spectrum and their proven ability to prevent antimicrobial resistance, but their clinical and commercial developments have certain limitations, such as sensitivity Proteases and high cost of peptide production. To overcome these problems, many researchers have tried to develop short active Peptides, and their mimic changes with better properties while maintaining the basic properties of natural AMPs such as cationic charge and an amphitheater structure. Biotic motifs which are identified sequences of natural AMPs may be used the backbone is synthetic substitutes of these peptides. It was determined that in many cases only small sequences of AMP are half active, it can be used as a backbone for the design of synthetic imitations of antimicrobial peptides (SMAMPs) with excellent features[7]. AMPs have attracted attention as a promising therapeutic

***Corresponding Author:** Shimon Shatzmiller, Department of Chemical Sciences, Ariel University, Ariel Israel, E-mail: shimon120@gmail.com

Sub Date: July 19th, 2019, **Acc Date:** July 22nd, 2019, **Pub Date:** July 26th, 2019

Citation: Shimon Shatzmiller (2019) The Quest for Selective Antimicrobial Agents The Antimicrobial Peptides and Their Surrogates Approach. BAOJ Microbiology 5: 050.

alternative to conventional antibiotics due to their broad antimicrobial activity and individual action against pathogens. However, the cost of high synthesis and systemic toxicity were problems for the further use of natural peptides. Recently, modification of natural AMPs has been synthesized and tested to be an effective strategy for reducing production cost and limiting toxicity (the peptidomimetics, Peptide surrogates) [8,9]. Biological activity assays showed that the short peptide analogs maintained the high intensity of microbial and limited the hemolytic activity induced by the mimic. This typical α-helical analog provided a suitable template for the study of quantitative-relationship relations and quantitative (QSARs) of α-helical peptides. Thus, , the high hydrophobic end of the analogs and a series of shorter peptides were created by erasing three dangerous N-specific amino acids at a time, determine the effects of chain length and hydrophobicity on the biological activity of peptides. Non-natural amino acids can function as potential biomimetic derivatives of natural amino acids Source for biomechanical peptides. A synthetic approach is presented here for the preparation of y-phosphono-N-methoxy amino acid. The research effort on the synthesis and biological value of amine phosphonates is performed in many places. The structure of our target molecules, for instance, has an amino acid Weinreb type amide moiety and ay -amino-phosphonate unit as a basic structure block. Although Weinreb amide part structure Andy -amino-phosphonates may act Different molecular mechanisms, the synergy between the two moieties may display an amazing microbial effect [10]. We can take the attack of a small peptide isolated from honey bees [11], apidaecin on bacterial cells as the working hypothesis: the mechanism of action in which apidaecin kill bacteria involves the initial state of the surface that does not explicitly bind peptides to an external membrane component. This binding is followed by the invasion of periplasmic space, and by a particular and essentially irreversible combination with a receptor / docking molecule which may be an element of permeability and permease type transport system on the internal membrane [12]. In the last stage, the peptide is translated into the inside of the bacterium, where it meets its ultimate purpose [13]. We examined a possible approach based on the microbial peptide (AMP) Substitutes offer assistance in such a situation [14,15]. We meant rational strategy based on the approximate mechanism of the antibacterial effect was which has been adopted to design microbial cations that are capable of cation binding the bacterial membrane to disrupt it [16]. Surface proteins are critical in determining detection properties of individual bacteria and their interaction with the environment. Survival of Gram-negative bacteria depending on the assembly of asymmetrical outer membrane, which creates a barrier that prevents the entry of toxic molecules include antibiotics. The outer leaflet of the outer membrane consists of lipopolysaccharide, which is done on the internal membrane pushed across Bridge proteins that extends to the outer and outer surfaces membranes. We have developed a fluorescent assay to Perform lipopolysaccharide (LPS) transport across the bridge Linking the proteoliposomes mimicking the internal and external Membranes[17].Because the structure of the cell surface[18,19,20] is the main characteristic distinguishes between positive bacteria and Gram-negative bacteria, the processes used to transport and attach these proteins show significant differences between these bacterial classes [21]. Proteins and hint he peptides the lipid membrane is a central aspect of many cellular signaling processes [22]. When these polypeptides reach their targets, their goals can include the external components of the bacteria, consisting mainly of lipopolysaccharide (LPS) of Gram-negative bacteria and lipoteichoic acid on positive grams Bacteria or cellular components, thus causing disruption.

Schematic drawing -a comparison of Gram (+) and Gram (-) bacteria cells

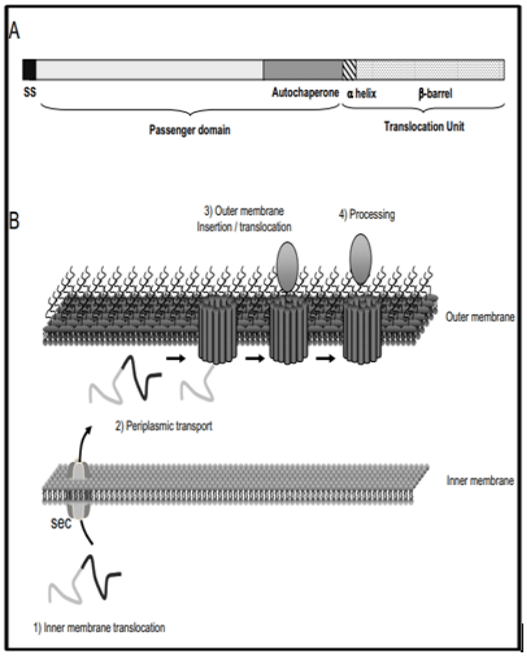


Figure 1: The organization and biogenes is of autopro-transformers organization and biogenesis of automatic transports. **A** typical organization of an automatic transporter (AT) which is a terminal sequence (N) terminal (SS), a passenger domain and a translocation unit (TU). The passenger segment includes part N terminal that carries the activity of the AT and C-terminal, known as the autochaperone domain, which is important for effective translation across the outer membrane. TU also has two separate areas; The terminal region N is structured as α-coil, whereas the terminal area C is structured as a **β**-barrel. **B** In the biogenesis of AT there are four main stages: translocation across the inner membrane, periplasmic transport, insertion into and translocation across the outer membrane, and finally, processing of the passenger domain. (Credit ref. [11])

Mechanism of action, in particular the unique "carpet" Shai-Matzuzaki-Huang [23] postulate gave hopes for a novel approach for

microbial eradication. But later it became apparent that microbes may be eradicated by many mechanisms, including receptor controlled [24]. There are new members, new mechanisms of action, new functions, and interesting applications of antimicrobial peptides reported. More than 100 new peptides were recorded into the Antimicrobial peptide database, increasing the total number of values entries up to 2493. The antimicrobial unique peptides have been identified to marine bacteria, fungi, plants. Clear environmental conditions Affect peptide activity or function. Known to bind to protein shock, are shown to inhibit protein synthesis. Model. The anti-microbial peptide is proved to have multiple hits on bacteria, including surface distribution. While changing cell surface to decrease cation binding peptide is a recognized resistance mechanism for pathogenic bacteria, it is also used for survival Strategy for commensal bacteria. We witnessed continued efforts Utilizing potential applications of antimicrobial peptides. We emphasize a 3D-based structure Design of bacteria and peptides and vaccines, surface coatings, supply systems, and microbial identification devices containing microbial peptides. Results also support because combined therapy is preferred over monotherapy in the treatment of biofilms. Urgent need for new agents that are effective against drug-resistant bacteria without contributing to resistance Development [25]. Antimicrobial peptides (AMPs) are promising romantic antibiotics because they exhibit a vast microbial spectrum, and are not easily objectionable. For clinical uses, it is essential to develop robust AMPs with less toxicity against the host Cells. We have designed short cationic peptide units consisting of two functional domains (KAAAK) embedded in a surrogate peptide composition. Due to their mechanism of action [26], antimicrobial peptides (AMPs) showed deficient, fungal bacteria viral resistance [1]. We designed and developed microbial [27] short peptides containing β rotation (head pin) [28] mimics as "homing [29]" moiety and two lysines indexed [30] term in their sequences with cationic amphibious structures based on imitation [31] of natural antimicrobial peptides occurring at deficient concentrations, less than 10 μm. These peptides are short Substitutes exhibit this vigorous antimicrobial activity against a wide variety of bacteria including E. coli and methicillin-resistant Staphylococcus aureus without harmful hemolytic activity and agglutination of erythrocytes [32]. MIC (minimal inhibitory concentration) [33] experiments Indicate that D-type and L-Freidinger-type β-turn-based cation peptides against almost identical host-like (CAMP) peptides both in the elimination of Gram + and of bacteria. Many studies assume, based on Merrifield's early work [34,35,36] on the effect of Cecropin's chiasm on ability, Eliminate bacteria. If the general structure of the peptide is the most important factor in the expression of activity, then any D-enantiomer may have the correct biological connections similar to those of the natural enantiomer respectively. This consideration is not true for receptor peptides [37].Synthetic D-enantiomers exhibit the same permeabilizing and biological activity as their natural counter parts. The fact that all D and L do the same elimination of bacteria, suggested the lack of a chiral transition [38] in the eradication process. This does not necessarily imply that there is no interaction between antimicrobial peptides and outer proteins moieties Affect vital processes for the survival of bacteria. This means that experiments have shown that D and L-amino acid versions Of antimicrobial peptides exhibit a similar affinity to target cells, suggesting that the stereoscopic receptors are not involved inTargeting pathogenic cells [39]. In fact, many mechanisms other than electrostatic attraction have been studied and formulated in. In recent years. These results indicate similar behavior of "artificial" and "natural"L-peptide substitutes when binding to a bacterial membrane have, however, hilarity sensitivity in human red blood cells (RBC)And thus a window of opportunity to reduce toxicity (hemolysis) by selecting the appropriate peptide Surrogate mother. The Peptide-Memory Design Principle offers significant flexibility and diversity in the new microbial formation Materials and their possible biomedical applications [16]. The potential of short-term β-turn AMPs for selectivity studies to avoid The elimination of a "friendly" microorganism is discussed on the basis of outer membrane bacterial proteins [40]. Peptide substitutes our studies may contribute to further understanding of how CAMPs sense the microbial membrane [18] as well as provide a new direction Develop new membrane disrupting agents [19,20]. The host structure has been identified which may connect to the exterior Membrane proteins of gram-negative bacteria [41], and changes the biological activity of microbial peptide imitations [42]. Different cell wall architecture [43] of Gram-positive bacteria and gram-negative may present a tool for selective selection of targets for elimination by microbial peptides and their hosts. N-methylation [44] may display a toolbox for designers and synthetic people to design and synthesize an urgent need for rapidly emerging bacterial epidemics, Agents of the romantic antibacterial. Unfortunately, Gs, (heterotrimeric G protein, alpha subunit) present poor selectivity between microbial and mammalian cells, limiting its use to topical applications. Recently, the effort has been devoted to the development of GS analogs with an improvement in its therapeutic index The antimicrobial and cytotoxic activity (eg, the multitudes) are cut off. In this journey, both β-strand and β-turn regions have been extensively improved in SAR studies that shed light on the factors that govern GS bioactivities, such as cationic, amphipathic, and nature Character, β sheet structure, ring size and global hydrophobicity [45].The penetration of AMPs into the membrane was a simulated computer. High-resolution structures and microbial orientations Peptide Piscidin 1 and Piscidin 3 in Bilayers Fluid reveal bias, kink, and Bilayer immersion [46]. Furthermore, the bacterial outer lipoprotein Lpp membrane does Gram-negative bacterial cell surface receptor for cationic microbial Peptides [47]. The outer membrane protein Lpp of Gram-negative Gram acts as a receptor for an antimicrobial peptide. Scientists identify and characterize the Lpp, which is responsible for the recognition of the antimicrobial action peptide. Lpp is a new target of microbial Peptide. The app may be used to the ligand to develop microbial materials.

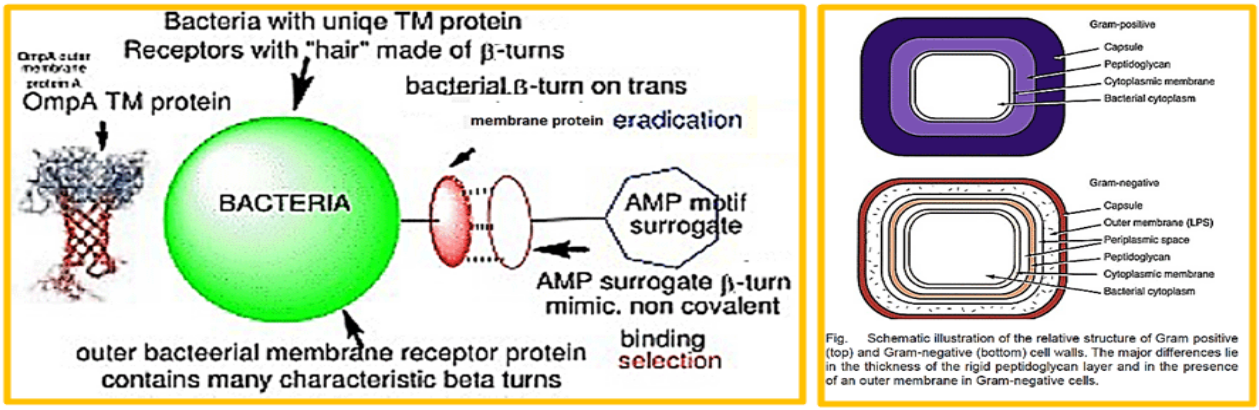


Figure 2:

+Schematic presentation of Gram +, Gram- and receptor-mediated eradication of bacteria

The penetration of the cell membrane in bacteria might be a clue for the preferential eradication of bacterial lines. Here we tackle the problem of cell wall penetration from two angles :Selection by receptors (bacteriocin-like activity [48]) and saturation [49,50].Another work of Rovers and co-workers, the association of AMP's PMAP-23 analog to E. coli cells was determined and found that mutation occurred only when peptides were fully charged to a saturated bacterial membrane (106-107 peptides related to each cell). These results lead the authors to conclude that the "carpet" model for disruption of artificial bilayers represents what happens to real bacteria [51]. It is now determined that simple small molecules based on simple motifs [52] can be prepared to eliminate Gram + as well as Gram-bacteria [53]. The next step is the stage of differentiation (attacking only the unwanted bacteria). The selectivity state we had in mind is to base the peptide-peptide to eliminate the β-phase emulations that are known to interact with cell wall proteins. In bacteria, especially in the outer part of the Trans membrane receptors [54]. Once the hosts settle in the inside of the outer membrane, a reliable ε of the lysine unit can "snorkel" [55]. Out and dislodge the membranes of gram-positive bacteria and Gram-negative bacteria [56]. The interactions of AMP with the membrane cannot be explained by continuous amino sequence pattern or motif; instead, they originate combination of structural physicochemical properties including size, composition residues, total charge, secondary structure, hydrophobicity and amphiphilic character. Pore formation by interacting with cell wall lipids and permeability changes and yet the permeability of the penetration of AMPs through the pore creates is determined by the effect on the elimination difference which is the result of disruption of the plasma membrane of the bacteria [57]. Moreover, interactions with many components that provide the architecture of the membranes are critical to antibacterial activity.

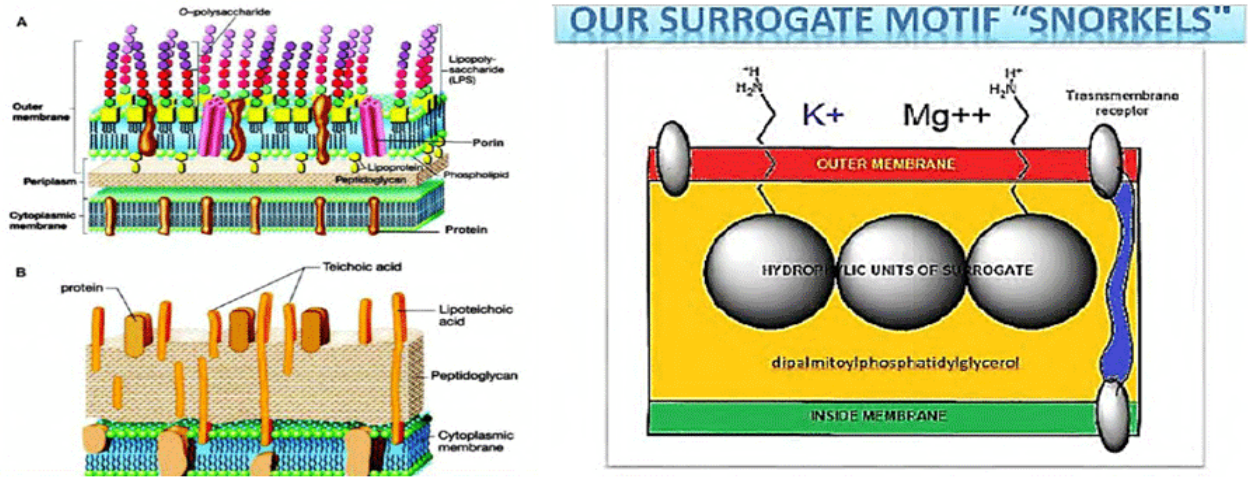


Figure 3: Cartoon display of Membranes (A) Gram-negative bacteria (B) Bacteria and Bacteria positive.

Gram-negative bacteria consists of two layers: the LPS-rich outer membrane Inner membrane is rich in PG anion. Gram-positive bacteria have a cell wall consisting of lipoteichoic acid and peptidoglycan and cytoplasmic membrane.credit ref. [58] Although the "carpet" postulate [59,60] excludes involvements of receptors in bacterial eradication and relies entirely on the cationic peptide's or surrogate, with the negatively charged outer membranes.

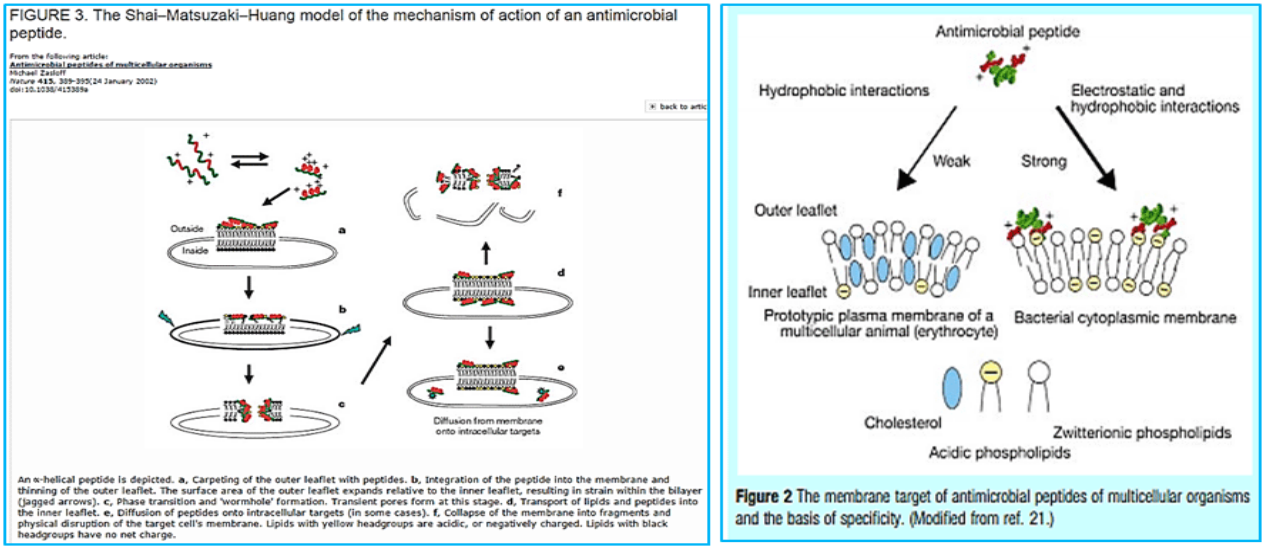


Figure 2 The membrane target of antimicrobial peptides of multicellular organisms and the basis of specificity. (Modified from ref. 21.)

Figure 4:

Nosocomial infection is the leading cause of death and increased morbidity among hospitalized patients worldwide. From data conducted by The World Health Organization (WHO) found 17 out of 100Hospitalized patients will be shown with infections acquired in the hospital both in developed and developing countries at any given time. Nosocomial Infections are already part of an epidemic. S. aureus and E.coli are the most common isolated bacteria that cause nosocomial infections. Among those that give therapeutic problems are cellulose resistance Staphylococci and Vancomycin are resistant to Enterococci. Need For novel agents active and urgent combat. The problem is in the Stage of environmental degradation, first near the health facilities. Antimicrobials, focusing on short antimicrobial peptide hosts, area promising outcome from this difficult situation. The use of peptidomimetics Or microbial synthetic peptides and substitutes, allows one to Mimic the natural structure by introducing non-natural amino acids. In this media, we present a finding that may lead to the chemical Contribution to combat. Preference of elimination of Gram (+) Bacteria is caused by a structural alternative of peptidomimetics Backbone. Different cell envelope architecture of two types of Bacteria permits the N-methylated 2-oxo pyrrolidone scaffoldenantiomer to evoke confirmative changes and change the preference toward the positive bacteria of the Gram-type. A drug that inhibits explicitly that traffic can act in several ways, for example, to affect the energy conversion mechanism (Which is currently unknown, but may be related to that used in mitochondrial ATPase, a mechanism of twin-arginine signal peptide identification, or perhaps a mechanism of peptide signal separation or trans membrane channel baskets in TatA. since the following two key activities involve recognition of peptide, antimicrobial peptide and can be the answer to provide specific inhibition of the path of the bacterium Tat. They allow the use of other material needed for cell metabolism. In the membrane, not each β barrel Proteins are transport proteins [61]. In most Trans membrane proteins, a polypeptide chain crosses the lipid bilayer in α-Helical [62].

Illustrated in Figure 10-38, the structure of which was determined by X-ray diffraction. (Credit ref. [18]).The transport through the channel can be rationalized by single group rotation (SGR) mechanism [63]

Some form smaller "barrels" that are filled with amino acid chains that project into the center of the "barrel". These proteins work like receptors or enzymes, here the barrel is used primarily as a rigid anchor that holds the protein in the membrane and promotes the Cytosolic loop regions form binding sites for specific intracellular molecules. Many studies assume, based on Merrifield's early work [34, 64] on the effect of Cecropin's chiasm on the ability to eliminate bacteria. Synthetic D-enantiomers exhibit the same permeabilizing and biological activity as their natural counterparts. The fact that all D and L do the same elimination of bacteria, suggested the lack of a chiral transition in the eradication process. This does not necessarily mean that there is no interaction between antimicrobial peptides and outer proteins moieties Affect vital processes for the survival of bacteria. This means that experiments have shown that D and L-amino acid versions. of antimicrobial peptides exhibit a similar affinity to target cells, suggesting that the stereoscopic receptors are not involved.

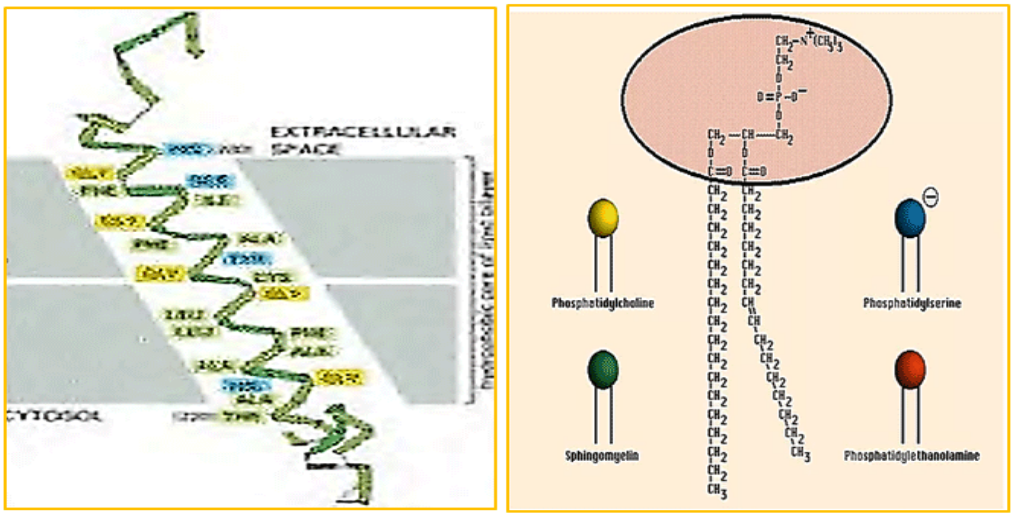
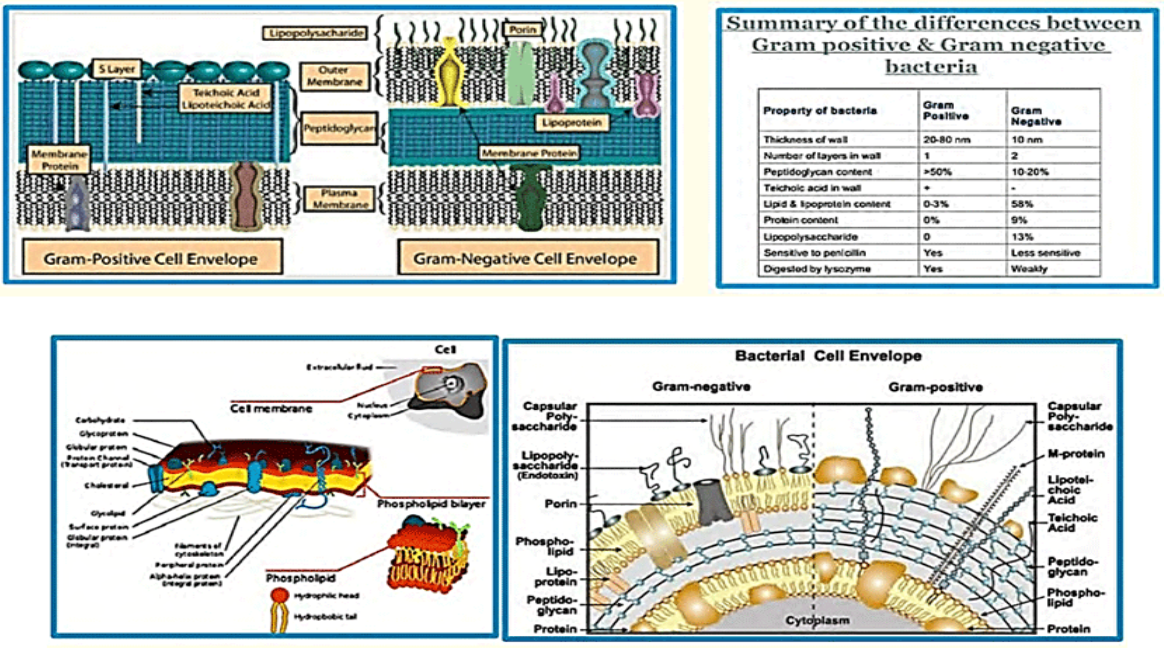


Figure 5: In green and yellow. The polypeptide segment shown is part of the bacterial photosynthetic reaction center
A phospholipid structure Only the α-carbon backbone of the polypeptide chain is shown, with the hydrophobic amino acids

Targeting pathogenic cells [22]. In fact, many mechanisms other than electrostatic attraction have been studied and formulated In recent years. A key stage in human trafficking [65], ex-endocytosis [66], viral entry and exit [67,68]. The purpose of many of these sequencesIs the thin fat itself, but some of them (such as peptide hormones [69] and bacterial toxins [70]) may work on proteins found into be a crust. Although the fundamental structure of biological membranes is provided by lipid layers [71] membrane proteins (AA typical plasma membrane is somewhere in between, with protein accounting for about 50-60% of its mass [72]). Protein, protein recognition, often observed interactions of antibodies with proteins and living organisms, is the main one the effects of still be fully understood and utilized by pharmaceutical researchers. The exchange, called the 3-D substitute domain, hasNow observed in a number of proteins and probably is a relatively common evolutionary mechanism for the generation of dimeric and Higher oligomeric forms of monomers Peptides and proteins are essential for many biological processes [73]. Completion, as dictated by the topology interface, seems to contribute to a specific interface.



Bacterial cell wall proteins

Figure 6:

Protein, protein recognition, often observed interactions of antibodies with proteins and living organisms, is the main one. The effects of still are fully understood and utilized by pharmaceutical researchers. The exchange, called the 3-D substitute domain, has been observed in a number of proteins and probably is a relatively common evolutionary mechanism for the generation of dimeric and higher oligomeric forms of monomers Peptides and proteins are essential for many biological processes [48]. Completion, as dictated by the topology interface, seems to contribute to a specific interface. Recently published articles on the interaction of synthetic amps and serum albumin protein [90]. Research in areas such as tuberculosis Mycobacterium is targeting tuberculosis and other microbial pathogens. Bacteria elimination. Here are the underlying mechanisms of antibiotics - action and resistance (see schematic presentation below):

1. Inhibition of cell wall synthesis (the most common mechanism)

2. Inhibition of protein synthesis (translation) (second-largest class)

3. Change of cell membranes

4. Inhibition of nucleic acid synthesis

5. Antimetabolite activity

The first obstacle that an anti-microbial agent must overcome when interacting with its target is the wall of the microbial cell [74].

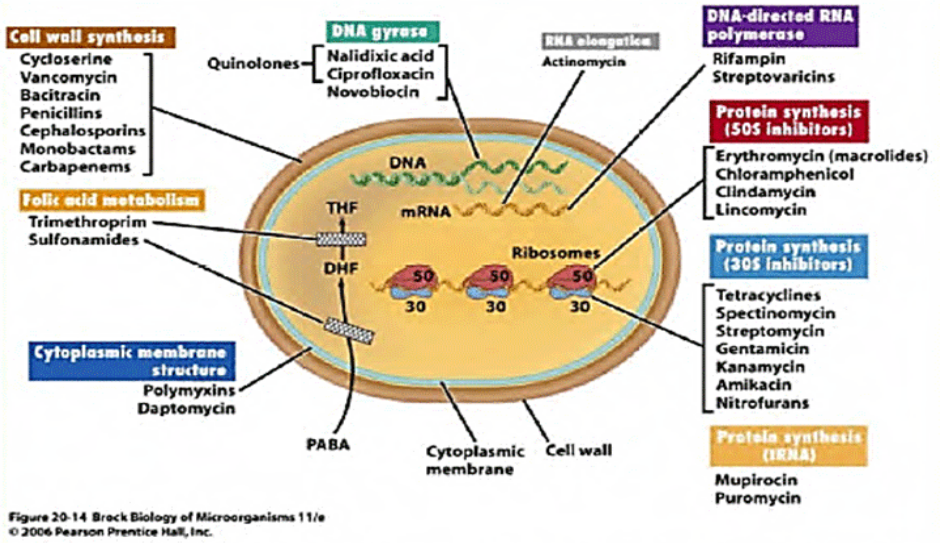


Figure 3. Classes of antibiotics/antibacterial agents and their modes of action on bacteria (Adopted from Labnotesweek4, 2013) [11].

Figure 7:

Action sites of antimicrobial substances [75]: all must cross the cell walls on antibacterial agents should be penetrated and in many cases cross the cell membrane. In most cases, it depends on energy [76]. This refers to many polypeptides that can provide an idea one of the main problems in the anti-bacterial campaign: the choice of the microorganism that hits the sole target of power Antimicrobial peptides and their hosts, mimicking them, leaving the contributing bacteria unharmed. We assume that our microbial Peptides penetrate directly into the cell wall [9] and do not undergo endocytrosys or assistance of transport [77]

Table 1:

	MIC (μM)a								
Sequence	*M. tuberculosis*	*M. smegmatis*	*P. aeruginosa*	*E. coil*	*S. enterica serovar Typhimurium*	*C. albicans*	*S. epidermidis*	*S. aureus*	*E. faecalis*
WKWLKKWIK	1.1	1.9	2.9	5.8	11.5	5.8	0.7 - 0.3	0.7	11.5
ILRWKWRWWRWRR	2.4	2.4	5.7	1.4	2.9	5.7	0.7	0.7	2.9
ILPWKWRWWKWRR	2.6	2.2	5.7	1.4	5.7	2.9	0.7	0.7	2.9
RWRRICWWWW	2.8	5.7	11.2	1.4	2.8	5.6	0.7	0.7	2.8
WRKFWKYLK	3.0	1.5	6.0	0.8	6.0	3.0	0.8	0.8	6.0

The bacterial cell membrane contains about a third of the proteins in the cell and is the site for crucial processes, such as active transport [78] of nutrients Waste, bacterial respiration, the formation of proton driving force in conjunction with respiratory enzymes, ATP generation, and cellular cell communications biofilms [79]. Antimicrobial peptides made by the host and the number of active bioactive molecules operating on the membrane, verify its significance as antibacterial The destination site. Cell wall proteins are a unique environment for bacteria and therefore can be applied to selecting one type of prokaryote since, and bind toAn agent who is able to eliminate the selected voltage [80]. Typically, membrane proteins are associated with Amphipols [81]. The detergents are used as molecular adapters to immobilize membrane proteins on solid supports.(Fig. 10). The interaction between the peptide ligands and their receptor targets usually involves β-turn structures [82]. However, poor bioavailability and negative pharmacokinetics significantly jeopardize the use of peptides as drugs. For these reasons, the peptides are replaced and complex to replace the peptide in its function, avoiding the drawbacks and implanting new traits that the original bio-active peptide did not acquire. Protein-protein interactions (PPIs) [83] regulate a wide range of cellular processes and attractive drug planning goals. Rotations are essential targets to mimic, both because they serve as peptide and protein recognition sites and because they allow a protein chain to fold it back to form a compact structure. Imitating β-turn can interact and bring recognition and association of proteins. It was also published that some of the capabilities of AMPs to combine with cell walls of bacteria are due to short peptide motifs PXXXP [84]. This may contribute to Catherine endothelium [85] for endocytosis, the structural and chemical requirement has been studied and the YXRF sequence combines a steady rotation such as the structural recognition motif endocytosis [86]. Some of the natural and synthetic microbial peptides were analyzed by NMR studies, which showed that, contrary to the reports of tachypneic magazines, I create a β-turn parallel-series connected to the β-turn II type even in aqueous solution. [87] Thus, the researchers examined the use of β- turn in protein-protein protocols that include trans membrane receptors in nerve cells in protein interactions, including β-turns [88].Many variants of the β-turn mimic, one of the nine-count β-turn types [89], have been applied so far in this area of study. It has been reported that surrogacy in the β-turn field of Gramicidin S increases biological activity [26]. One can read about.

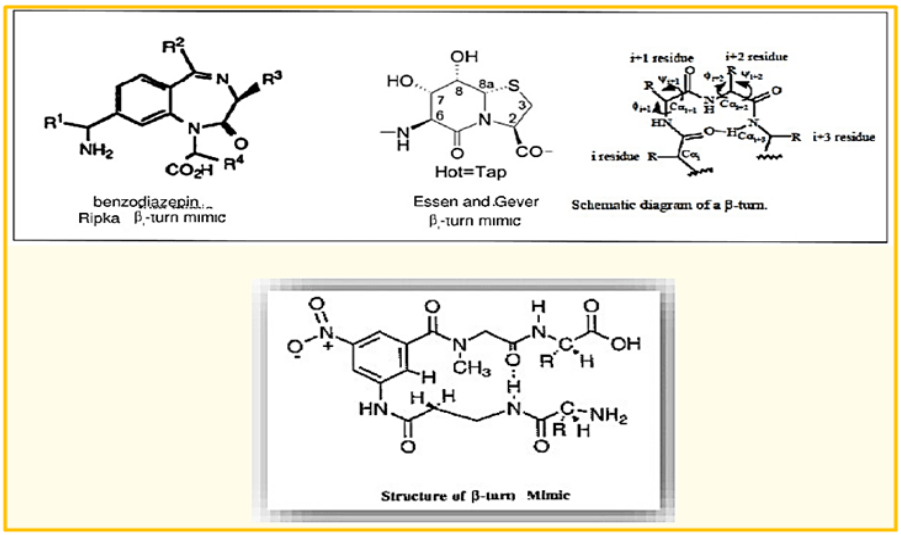


Figure 8:

Benzodiazepines, β-turn to mimic "hot = press" for example [90]. There is a growing demand for new antimicrobial agents for treatment, but also for hygiene and agriculture, soil sterilization, for example. A class of compounds to focus on is a growing group of isolated polypeptides as part of the host defense systems of all organisms on the planet (antimicrobial peptides). Varieties of harmful bacteria become more resistant to drugs, but also live in the environment, in the same organism, as a useful and necessary additional pet of microorganisms existing in human intestines, "good" different strands of raids, Bacteroidetes, Actinobacteria, and Proteobacteria for example. We want to selectively eliminate the "bad" (Pseudomonas aeruginosa, Escherichia coli (E. coli), Clostridium hard, Burkholderiacepacia, Klebsiella infection, Staphylococcus aureus, Streptococcus pyrogens, Mycobacterium Tuberculosis, Acinetobacter baumannii, Microorganisms and leave the "useful" It was determined that simple small molecules based on simple motifs could be ready and mimic Gram (+) and Gram (-) bacteria. The next step is the stage of differentiation (to attack only the unwanted bacteria.) The selectivity method we discussed is to base the peptide substitutes Bβ known to be associated with proteins in the cell wall. In bacteria, especially in the outer part of Trans membrane receptors [91], after Soldiers settle into the inside of the outer membrane, E reliable unit lysine can "snorkel"

[92]. From data conveyed by The World Health Organization (WHO) found 17 out of 100Hospitalized patients will be shown with infections acquired in the hospital both in developed and developing countries at any given time. Nosocomial Infections are already part of an epidemic. S. aureus and E.coli are the most common isolated bacteria that cause nosocomial infections. Among those that give therapeutic problems are cellulose resistance Staphylococci and Vancomycin are resistant to Enterococci. Need For novel agents active and urgent combat. The problem is inThe Stage of environmental degradation, first near the health facilities. Antimicrobials, focusing on short antimicrobial peptide hosts, area promising outcome from this difficult situation. The use of peptidomimetics or microbial synthetic peptides and substitutes, allows one to mimic the natural structure by introducing non-natural amino acids. In this media, we present a finding that may lead to the chemical Contribution to battle. Preference of elimination of Gram-positive Bacteria is caused by a structural alternative of peptidomimetics Backbone. Different cell envelope architecture of two types of Bacteria permits the N-methylated 2-oxo pyrrolidone scaffoldenantiomer to evoke conformation changes and change the preference toward the positive bacteria of the gram. An amino acid containing amino acid Peptide inhibitor Aβ (1-40).

Table 2:

Gram-negative	Gram-positive	Property
10 nm	20-80 nm	Thickness of wall
2	1	Number of layers in wall
10-20%	>50%	Peptidoglycan content
-	+	Teichoic acid in wall
58%	0-3%	Lipid and lipoprotein content
9%	0%	
13%	0%	Protein content
Less sensitive	Yes	Lipopolysaccharide
Weakly	Yes	Sensitive to penicillin
		Digested by lysozyme

The table summarizes the difference between Gram-Negative and Gram-positive Cell walls [93]. Gram-negative bacteria are usually less sensitive to inhibitor cell wall synthesis than positive bacteria caused due to the presence of an outer cover around the cell wall. Porin channels Present Gram-negative bacteria which can prevent the entry of pests Chemicals and antibiotics like penicillin. These channels can also be expelled out Antibiotics do much more difficult to treat compared with Gram-positive Bacteria [94]. Surface proteins are critical in determining the detection properties of individual bacteria and their interaction with the environment. Because cell surface structure is the main characteristic that distinguishes between a harmful bacterium and a Gram-negative gram, the processes used to transport and bind these proteins to show significant differences between these bacterial classes [95]. Proteins and peptides diffusion within lipid membranes are a vital aspect of many cellular signaling processes [10]. When these polypeptides reach their targets, their targets can include the external components of the bacterium, consisting mainly of lipopolysaccharide (LPS) of Gram-negative bacteria of a lipoteichoic acid on gram-positive bacteria or intracellular components, thereby disrupting the service of AMPs as potential drugs are currently recognized By scientists [96]. However, there are some drawbacks that need the attention of researchers: a complete understanding of how these AMPs eliminate the bacteria; The understanding of the selectivity of different AMP for bacterial mammalian membranes is of interest in the development of these peptides as new antibacterial agents; Design and synthesis of substitutes and their biological relevance assessment; To develop new types of selective materials that will enable the elimination of harmful bacteria and will not harm bacteria living with us in vital symbiosis [97,98]. Recently evidence has been shown that manslaughter occurs only when bacteria The cell membrane is wholly saturated with AMPs. This situation is achieved for all bacteria. However, since harmful bacteria caused The outer membrane is dense, packed in different proteins (up to 50% of the total membrane weight), compared to only 15% of the surface A Gram-positive layer, this requires more energy saturation in Gram-negative than In Gram-positive [99] (see Table 1 above). The cell wall of Gram-positive bacterium and the outer membrane of Gram-negative bacteria contain lipid molecules of anions [100]. Gram-positive bacteria are the lipo-teichoic acid (LTA) and LPS that may compete with the plasma membrane for interaction with AMPs. Not only the cell walls, but also the plasma membrane targets for its AMP or surrogate. The matrix is generated by a different phospholipid bilayer in the head group and the vehicle composition acid contributes to a mechanical variety of AMPs against microbial cells [101]. We observed that the elimination of the Gram-positive bacteria (S. aureus) is affected by the introduction of the N-CH3 transformation into the molecule, which increases activity by a factor of three. As in AMPs, hilarity is not expected to make any difference in the elimination of bacteria. The elimination of Gram-negative bacteria is the same in almost all 4 substitutions (Table 2). The changes in the molecular properties shown by N-methylation do not affect the way the host kills the Gram-negative bacteria. On the other hand, the elimination of the positive gram is one of the determining events that is the entry into the bacterial membrane [36]. A membrane disorder by an antimicrobial agent involves at least three stages [102]. First, a cationic peptide can detect coat and the surface of anionic bacteria. With the classical amphipathic helical structure, this cation peptide prefers to target the anionic bacterial membrane. Second, the agent binds to the outer membranes and crosses the outer membrane. Third, the peptide reaches the inner membrane. This initially binds to the corresponding surface membrane, which is the basis for the carpet model at high concentrations; the peptide may disrupt the

membrane by micellization. Alternatively, the peptide may take a vertical position to form a pore. Transfer of solvents through Daria is usually carried out through specific active transport systems (eg, "worms") that require energy [103]. The transport of substitutes from the outer membrane organized to the target wall in the inner cell wall is different for two types of bacteria. The introduction of the N-CH3 unit to the pentapeptides substitutes 3 and 4 stiffen the structure, thereby increasing the demand for energy saturation. The fraction of this energy in negative Gram is smaller than in gram-positive due to composition and membrane packing. It is easier for N-CH3to penetrate the outer membrane with positive bacteria in Gram and Gram-negative. Since saturation is achieved in a positive gram with fewer energy requirements, Gram vs. Negative are deleted preference.

Conclusions

Gram-positive bacteria are more natural to penetrate because the outer membrane is weak in membrane proteins. In such circumstances, small energy changes can be significant for the agent's travel into the outer membrane. N-methylated analogs are less flexible and therefore penetrate the inner membrane easier. Finally, after the replacements settle in the inside of the outer membrane, the Lysine's reliable unit can "snorkel" out and break down the membranes of Gram-positive bacteria and Gram-negative bacteria. [46] The interactions of AMP with the membrane cannot be explained by a specific pattern in amino acid sequence or motif; they derive from a combination of physical and structural properties, including size, the composition of residues, total loading, secondary structure, hydrophobicity and amphibious nature. Creating porosity by interacting with cell wall lipids and permeability changes and yet the permeability of the penetration of AMPs through the pore creates is determines the effect on the elimination difference which is the result of the disruption of the plasma membrane of the bacteria. Moreover, interactions with many components that provide the architecture of the membranes are critical to antibacterial activity. From our study, we conclude that the venerability of bacteria may be dependent on a small structural variation in the composition of the biocide. Protein-Protein Interfaces [104,105] Interactions can be satisfied by adding a second copy of the interface domain to a monolithic polypeptide in such a way as to allow it to interact with the original interface. (The second strategy has been transferred by Mossing and Sauer when they are connected via a β-turn, a partial copy of the ribbon-interface β-crop - protects the DNA protein - until the end of the whole copy. The second copy loop back interacting with the rest of the protein to create a stable monomer). Modified cell wall architecture of Gram positive and Gram negative may present a tool for the selective selection of targets for elimination by antimicrobial peptides and their substitutes. B and N methylation may present a toolbox for designers and synthetic people to shape and synthesize

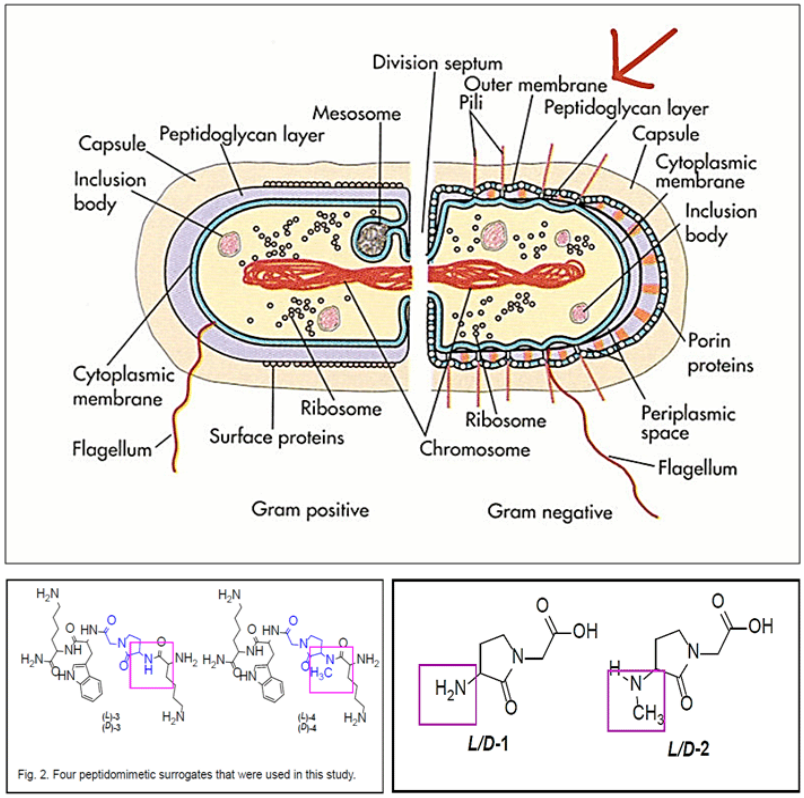


Figure 9:

the necessary impulse for rapidly emerging bacterial epidemics, the antiviral agents of romance. There exist significant architectural differences between Gram (+) and Gram (-) bacteria. A biocide (fig. 2) that has to deal with Grarm (+) bacteria needs less energy to deal with the eradication process. The bactericide has to cross one outer membrane and penetrate the cytoplasmic (peptidoglycan) soft layer to reach the killing position. This travel is sensitive to small structural modification in the penetrating bactericide. In contrast to that, the eradication of Gram(-) bacteria involved the crossing of the bacterial capsule, porin layer, the outer membrane the inner cell wall (cytoplasmic membrane) that is loaded with protein molecule and then to cross the Gram(-) inner wall to reach the killing zone. This needs a considerably more significant amount of energy as compared to Gram+_bacterial penetration.

Table 3: Antimicrobial activity against gram-negative and gram-positive bacteria and hemolytic activity of the AMP surrogates

	Sequence	MIC (μg/mL)		HC_{50} (μg/mL)
		S. aureus	E. coli	
(L)-3	(L)-Lys-(L)-1-(L)-Trp-(L)-Lys-NH_2	100	31.3	>1000
(D)-3	(D)-Lys-(D)-1-(D)-Trp-(D)-Lys-NH_2	100	50	>1000
(L)-4	(L)-Lys-(L)-2-(L)-Trp-(L)-Lys-NH_2	31.3	62.5	>1000
(D)-4	(D)-Lys-(D)-2-(D)-Trp-(D)-Lys-NH_2	31.3	75	>1000

We have found that Gram+ bacteria are more sensitive to structural modifications, achieved by N-methylation. Whereas dealing with gram- bacteria, such architectural changes are negligible. It is just a hard job for the biocide molecule to kill the Gram (-) bacteria [96].

References

1. Awany D, Allali I, Dalvie S, Hemmings S, Mwaikono KS, et al (2019) "Host and Microbiome Genome-Wide Association Studies: Current State and Challenges"; Current State and Challenges. Front. Genet 9: 637.

2. Thaiss CA, Elinav E (2017)" The remedy within: will the microbiome fulfill its therapeutic promise?"; J MolMed 95(10): 1021-1027.

3. Jenssen H, Hamill P, Hancock RE (2006)" Peptide Antimicrobial Agents"; Clin Microbiol Rev 19(3): 491-511.

4. Brown DG, Soto R, Yandamuri S, Stone C, Dickey L, et al (2019)" The microbiota protects from viral-induced neurologic damage through microglia-intrinsic TLR signaling" .elife 8:e47117.

5. Sato H, Feix JB, (2006) "Peptide–membrane interactions and mechanisms of membrane destruction by amphipathic α-helical antimicrobial peptides"; Biochimica Biophysica Acta 1758(9): 1245-1256.

6. Lyu Y, Yang Y, Lyu X, Dong N, Shan A (2016)" Antimicrobial activity, improved cell selectivity and mode of action of short PMAP-36-derived peptides against bacteria and Candida"; Sci Rep 6: 27258.

7. Shatzmiller S, Zats G, Malka R, Brider T, Lapidot I Krieger R (2017) "Antibacterial Peptide Surrogates A Brief Review". EC Pharmacology and Toxicology 4(3): 94-111.

8. Lv Y, Wang J, Gao H, Wang Z, Dong N, et al (2014)"Antimicrobial properties and membrane-active mechanism of a potential alpha-helical antimicrobial derived from cathelicidin PMAP-36". PLos one 9(1): e86364.

9. Díaz M, Jiménez JM, Ortuño RM (1997)" Enantioselective synthesis of novel, highly conformationally constrained peptide surrogates"; Tetrahedron 8(4): 2465-2471.

10. Shaul M, Krieger R, Zats G, Lapidot I, Feit BM, et al (2019)" "Preparation of γ-(N·methoxy)-Amino-Phosphonic Acids Dimethyl Esters as Precursors to Biomimetic Peptides". EC Pharmacology and Toxicology 7(4): 257-276.

11. Carnicelli V, Lizzi A, Ponzi A, Amicosante G, Bozzi A, et al (2013) Interaction between antimicrobial peptides (AMPs) and their primary target, the biomembranes. Microbial Pathogens and Strategies for Combating Them: Science Technology, and Education 2: 1123-1134.

12. White TR, Renzelman CM, Rand AC, Rezai T, McEwen CM, et al (2011) On-resin N-methylation of cyclic peptides for discovery of orally bioavailable scaffolds. Nature chemical biology 7(11): 810-817.

13. Wilmes M, Cammue BP, Sahl HG, Thevissen K (2011) Antibiotic activities of host defense peptides: more to it than lipid bilayer perturbation. Natural product reports 28(8): 1350-1358.

14. Boman H (2003) Antibacterial peptides: basic facts and emerging concepts. Journal of internal medicine 254(3): 197-215.

15. Fjell CD, Hiss JA, Hancock RE, Schneider G (2012) Designing antimicrobial peptides: form follows function. Nature reviews Drug discovery 11(1): 37-51.

16. Fraser V, Ho B, Ding J (2004) De novo design of potent antimicrobial peptides. Antimicrobial agents and chemotherapy 48(9): 3349-3357.

17. Xie R, Taylor RJ, Kahne D (2018)" Outer Membrane Translocon Communicates with Inner Membrane ATPase to Stop Lipopolysaccharide Transport": J. Am. Chem. Soc 140(40): 12691-12694.

18. Navarre WW, Schneewind O (1999)" Surface Proteins of Gram-Positive Bacteria and Mechanisms of Their Targeting to the Cell Wall Envelope"; Microbiol Mol Biol Rev 63(1): 174-229.

19. Rutherford N, Michael Mourez (2006)" Surface display of proteins by Gram-negative bacterial auto transporters"; Microbial Cell Factories 5:22.

20. Caitlin Mcdermott-Murphy, Harvard University

21. Jean N, Bougault C, Simorre JP," The Structure of Bacterial Cell Wall"

22. Weiß K, Neef A, Van Q, Kramer S, Gregor I, et al. (2013) Quantifying the diffusion of membrane proteins and peptides in black lipid membranes with 2-focus fluorescence correlation spectroscopy. Biophysical journal 105(2): 455-462.

23. Shai Y (2002) "Mode of action of membrane active antimicrobial peptides" Biopolymers 66(4): 236-248.

24. Wang G, Mishra B, Lau K, Lushnikova T, Golla R, et al (2015)" Antimicrobial Peptides in 2014"; Pharmaceuticals 8(1): 123-150.

25. Shatzmiller S, Gellermann G, Albeck A, Malka R, Malka D, et al (2018)" Bacteria Cell Wall Polypeptides as Targets for the Selectivity in Antimicrobial Peptides as Antibiotic compounds", EC Pharmacology and Toxicology 6(7): 559-579.

26. Shai-Matsuzaki-Huang (2008) "Biotechnologically Engineered Antimicrobial Peptides Hope Against Multiresistant Bacteria".

27. Malanovic N, Lohner K (2016) "Antimicrobial Peptides Targeting Gram-Positive Bacteria" Pharmaceuticals (Basel) 9(3): 59.

28. Wu M, Maier E, Benz R, Hancock RE (1999) "Mechanism of Interaction of Different Classes of Cationic Antimicrobial Peptides with Planar Bilayers and with the Cytoplasmic Membrane of Escherichia coli". Biochemistry 38(22): 7235-7242.

29. Ellerby HM, Arap W, Ellerby LM, Kain R, Andrusiak R, et al(1999) "Anti-cancer activity of targeted pro-apoptotic peptides". Nature Medicine 5(9): 1032-1038.

30. Zats GM, Kovaliov M, Albeck A, Shatzmiller S (2015): "Antimicrobial benzodiazepine-based short cationic peptidomimetics". Journal of Peptide Science 21(6): 512-519.

31. Chongsiriwatana NP, Patch JA, Czyzewski AM, Dohm MT, Ivankin A, et al (2008) "Peptoids that mimic the structure, function, and mechanism of helical antimicrobial peptides". PNAS 105(8): 2794-2799.

32. Marikovsky Y, Danon D, Katchalsky (1966) Agglutination by polylysine of young and red blood cells". Biochimica et Biophysica Acta 124: 154-I59.

33. Andrews JM (2001) "Determination of minimum inhibitory concentrations". Journal of Antimicrobial Chemotherapy 48(S1): 5-16.

34. Merrifield RB, Juvvadi P, Andreu D, Ubach J, Boman A (1995) "Retro and retroenantio analogs of cecropin-melittin hybrids". Proceedings of the National Academy of Sciences of the United States of America 92(8): 3449-3453.

35. Wade D, Boman A, Wåhlin B, Drain CM, Andreu D, et al (1990) "All-D amino acid-containing channel-forming antibiotic peptides". Proceedings of the National Academy of Sciences of the United States 87(12): 4761-4765.

36. Faingold O, Ashkenazi A, Kaushansky N, Ben-Nun A, Shai Y (2013) "An Immunomodulating Motif of the Hiv-1 Fusion Protein is Chirality-Independent Implications for Its Mode of Action". Journal of Biological Chemistry 288(46): 32852-32860.

37. Morley JS, Tracy HJ, Gregory RA "Structure–Function Relationships in the Active C-Terminal Tetrapeptide Sequence of Gastrin"; Nature 207(5004): 1356-1359.

38. Bessalle R, Kapitkovsky A, Gorea A, Shalit I, Fridkin M (1990)" All-D-magainin: chirality, antimicrobial activity and proteolytic resistance"; FEBS Lett 274(1-2): 151-5.

39. Yeaman MR, Yount NY (2003) "Mechanisms of antimicrobial peptide action and resistance". Pharmacological Reviews 55(1): 27-55.

40. Pawelek PD, Croteau N, Ng-Thow-Hing C, Khursigara CM, Moiseeva N, et al (2006) "Structure of TonB in Complex with FhuA, E. coli Outer Membrane Receptor". Science 312(5778):1399-1402.

41. Thomas G Slama (2008) "Gram-negative antibiotic resistance: there is a price to pay". Critical Care 12(4): S4.

42. Sivertsen A, Isaksson J, Leiros HS, Svenson J, Svendsen JS, et al (2014) "Synthetic cationic antimicrobial peptides bind with their hydrophobic parts to drug site II of human serum albumin". BMC Structural Biology 14: 4.

43. Chatterjee J, Laufer B, Kessler H (2012) Synthesis of N-methylated cyclic peptides. Nature protocols 7(3): 432-444.

44. Chatterjee J, Gilon C, Hoffman A, Kessler H (2008) "N-methylation of peptides: a new perspective in medicinal chemistry". Accounts of chemical research 41(10): 1331-1342.

45. Solanas C, de la Torre BG, Fernández-Reyes M, Santiveri CM, Jiménez MA, et al. (2010) "Sequence Inversion and Phenylalanine Surrogates at the β-Turn Enhance the Antibiotic Activity of Gramicidin S". Journal of Medicinal Chemistry 53(10): 4119-4129.

46. Perrin BS, Tian Y, Fu R, Grant CV, Chekmenev EY, et al (2014) "High-Resolution Structures and Orientations of Antimicrobial Peptides Piscidin 1 and Piscidin 3 in Fluid Bilayers Reveal Tilting, Kinking, and Bilayer Immersion". Journal of the American Chemical Society 136(9): 3491-3504.

47. Chang TW, Lin YM, Wang CF, Liao YD (2012) "Outer Membrane Lipoprotein Lpp Is Gram-negative Bacterial Cell Surface Receptor for Cationic Antimicrobial Peptides". The Journal of Biological Chemistry 287(1): 418-428.

48. Paul D. Cotter (2014) " An 'Upp'-turn in bacteriocin receptor identification"; Molecular Microbiology 92(6): 1159-1163.

49. Hollmann A, Martinez M, Maturana P, Semorile LC, Maffia PC (2018) Antimicrobial Peptides: Interaction With Model and Biological Membranes and Synergism With Chemical Antibiotics"; Front Chem 6: 204.

50. Schulz GE ((2002))" The structure of bacterial outer membrane proteins"; Biochimica et Biophysica Acta 1565(2): 308- 317.

51. Roversi D, Luca V, Aureli S, Park Y, Mangoni ML (2014) "How many antimicrobial peptide molecules kill a bacterium? The case of PMAP-23". ACS Chem. Biol. 9(9): 2003-2007.

52. Ryan L, Lamarre B, Diu T, Ravi J, Judge PJ, et al (2016) "Anti-antimicrobial Peptides folding-mediated host defense antagonists". The Journal of Biological Chemistry 288(28): 20162-72.

53. Toke O (2005) "Antimicrobial Peptides: New Candidates in the Fight Against Bacterial Infections". Biopolymers (Peptide Science) 80(6): 717-735.

54. Arora A, Abildgaard F, Bushweller JH, Tamm LK (2001) "Structure of outer membrane protein A transmembrane domain by NMR spectroscopy". Nature structural biology 8(4): 334-338.

55. Strandberg E, Killian JA (2003) "Snorkeling of lysine side chains in transmembrane helices: how easy can it get?" FEBS Letters 544(1-3): 69-73.

56. Koebnik R, Locher KP, Van Gelder P (2000) "Structure and function of bacterial outer membrane proteins: barrels in a nutshell". Molecular Microbiology 37(2): 239-253.

57. Palermo EF, Kuroda K (2010) "Structural determinants of antimicrobial activity in polymers which mimic host defense peptides". Applied Microbiology and Biotechnology 87(5): 1605-1615.

58. Mosier-Boss PA (2017) " Review on SERS of Bacteria"; Biosensors 7(4): E51

59. Gazit E, Miller IR, Biggin PC, Sansom MS, Shai Y (1996) "Structure and orientation of the mammalian antibacterial peptide cecropin p1 within phospholipid membranes". J. Mol. Biol 258: 860-870.

60. Zasloff M (2002) "Antimicrobial peptides of multicellular organisms"; Nature 415(6870): 389-395.

61. Dawson RJ, Locher KP (2006) "Structure of a bacterial multidrug ABC transporter". Nature 443(7108): 180-185.

62. de Planque MR, Greathouse DV, Koeppe RE, Schäfer H, Marsh D et al. (1998) "Influence of Lipid/Peptide Hydrophobic Mismatch on the Thickness of Diacyl phosphatidylcholine Bilayers. A ^{2}HNMR and ESR Study Using Designed Transmembrane R-Helical Peptides and Gramicidin A". Biochemistry 37(26): 9333-9345.

63. Edward M Kosower (1983) "Partial tertiary structure assignments for the ,8-, y- and Subunits of the acetylcholine receptor on the basis of the hydrophobicity of amino acid sequences and channel location using single group rotation theory". FEBS Letters 155(2): 245-247.

64. Faingold O, Ashkenazi A, Kaushansky N, Ben-Nun A, Shai Y (2013) "An Immunomodulating Motif of the Hiv-1 Fusion Protein is Chirality-Independent Implications for Its Mode of Action". Journal of Biological Chemistry 288(46): 32852-32860.

65. Jung JJ, Inamdar SM, Tiwari A, Choudhury A (2012) "Regulation of intracellular membrane trafficking and cell dynamics by syntaxin-6".

Bioscience Reports 32(4): 383-391.

66. Koch M, Holt M (2012) "Coupling exo- and endocytosis: An essential role for PIP (2) at the synapse". Biochimica et Biophysica Acta 1821(8): 1114-1132.

67. Galdiero S (2009) "Editorial: Developments in membrane fusion". Protein and Peptide Letters 16(7): 711.

68. Falanga A, Cantisani M, Pedone C, Galdiero S (2009) "Membrane fusion and fission: Enveloped viruses". Protein and Peptide Letters 16(7): 751-759.

69. Romano R, Dufresne, Prost MC, Bali JP, Bayerl TM, et al (1993) "Peptide hormone-membrane interactions. Intervesicular transfer of lipophilic gastrin derivatives to artificial membranes and their bioactivities". Biochimica ET Biophysica Acta 1145(2): 235-242.

70. Galdiero S, Galdiero M, Pedone C (2007) "Beta-Barrel membrane bacterial proteins: Structure, function, assembly and interaction with lipids". Current Protein and Peptide Science 8(1): 63-82.

71. Matsuzaki K (2009) "Control of cell selectivity of antimicrobial peptides". Biochimica et Biophysica Acta 1788(8): 1687-1692.

72. Osborn MJ, Gander VE, Parisi E, Carson J (1972) "Mechanism of Assembly of the Outer Membrane of Salmonella typhimurium". The Journal of Biological Chemistry 247(12): 3962-3972.

73. Nikaidol H, Vaara M (1985) "Molecular Basis of Bacterial Outer Membrane Permeability". Microbiological Reviews 49(1):1-32.

74. Bbosa GS, Mwebaza N, Odda J, Kyegombe DB, Ntale M (2014) "Antibiotics/antibacterial drug use, their marketing and promotion during the post-antibiotic golden age and their role in emergence of bacterial resistance". Health 6(5): 410-425.

75. Yan J, Wang K, Dang W, Chen R, Xie J (2013) "Two Hits Are Better than One: Membrane-Active and DNA Binding Related Double-Action Mechanism". Antimicrobial Agents and Chemotherapy 57(1): 220-228.

76. Edwin S, Amersfoort V, Van Berkel TJC, Kuiper J (2003) "Receptors, Mediators, and Mechanisms Involved in Bacterial Sepsis and Septic Shock". Clinical Microbiology Reviews 16(3): 379-414.

77. Pooga M, Hällbrink M, Zorko M, Langel U (1998) "Cell penetration by transportan". FASEB Journal 12(1): 67-77.

78. Melville S, Craig L (2013) "Type IV Pili in Gram-Positive Bacteria". Microbiology and Molecular Biology Reviews 77(3): 323-341.

79. Heilmann C, Goetz F (2010) "Cell-Cell Communication and Biofilm Formation in Gram-Positive Bacteria". Bacterial Signaling Edited by Reinhard Krämer and Kirsten Jung Copyright WILEY-VCH Verlag GmbH and Co. KGaA, Weinheim 3: 323-341.

80. Hurdle JG, O'Neill AJ, Chopra I, Lee RE (2011) "Targeting bacterial membrane function: an underexploited mechanism for treating persistent infections". Nat Rev Microbiol 9(1): 62-75.

81. Tribet C, Audebert R, Popot JL (1996) "Amphipols: Polymers that keep membrane proteins soluble in aqueous solutions". Proceedings of the National Academy of Sciences USA 93(26): 15047-15050.

82. Kee KS, Jois SD (2003)" Design of β-turn Based Therapeutic Agents**"** Curr Pharm Des 9(15): 1209-1224.

83. Srinivasulu YS, Wang JR, Hsu KT, Tsai MJ, Charoenkwan P, (2015)" Characterizing informative sequence descriptors and predicting binding affinities of heterodimeric protein complexes"; BMC Bioinformatics 16(Suppl18): S14.

84. Yang ST, Jeon JH, Kim Y, Shin SY, Hahm KS, et al (2006) "Possible Role of a PXXP Central Hinge in the Antibacterial Activity and Membrane Interaction of PMAP-23, a Member of Cathelicidin Family". Biochemistry 45(6): 1775-1784.

85. Youtube presentation of Clathrin endocytosis: L.

86. Collawn JF, Stangel M, Kuhn LA, Esekogwu V, Jing SQ, et al (1990) "Transferrin Receptor Internalization Sequence YXRF Implicates a Tight Turn as the Structural Recognition Motif for Endocytosis". Cell 63(5): 1061-1072.

87. Tamamura H, Kuroda M, Masuda M, Otaka A, Funakoshi S, et al (1993) "A comparative study of the solution structures of tachyplesin I and a novel anti-HIV synthetic peptide, T22 ([Tyr 5'12, Lys7]-polyphemusin II), determined by nuclear magnetic resonance". Biochimica et Biophysica Acta 1163(2): 209-216.

88. Burgess K (2001) "Solid-Phase Syntheses of β-turn Analogues to Mimic or Disrupt Protein-Protein Interactions". Accounts of Chemical Research 34(10): 826-835.

89. The nine β-turn types with their dihedral angles.

90. Eckhardt B, Grosse W, Essen LO, Geyer A (2010) "Structural characterization of a β-turn mimic within a protein-protein interface". PNAS 107(43): 18336-18341.

91. Wang G, Mishra B, Epand RF, Epand R (2014) "High-quality 3D structures shine light on antibacterial, anti-biofilm and antiviral

activities of human cathelicidin LL-37 and its fragments". Biochimica et Biophysica Acta 1838(9): 2160-2172.

92. Che Y, Marshall GR (2008) "Privileged scaffolds targeting reverse-turn and helix recognition". Expert Opinion on Therapeutic Targets 12(1): 1-14.

93. Brown L, Wolf JM, Prados-Rosales R, Casadevall A (2015),"Through the wall: extracellular vesicles in Gram-positive bacteria, mycobacteria and fungi". Nature Reviews Microbiology 13(10): 620-630.

94. Nawrocki KL, Crispell EK, McBride SM (2014) "Antimicrobial peptide resistance mechanisms of gram-positive bacteria". Antibiotics 3(4): 461-492.

95. Scott JR, Barnett TC (2006) Surface proteins of gram-positive bacteria and how they get there. Annu. Rev. Microbiol 60: 397-423.

96. Saravolatz LD, Pawlak J, Johnson L, Bonilla H, Fakih MG, et al. (2012) "In vitro activities of LTX-109, a synthetic antimicrobial peptide, against methicillin-resistant, vancomycin-intermediate, vancomycin-resistant, daptomycin-nonsusceptible, and linezolid-no susceptible Staphylococcus aureus". Antimicrobial agents and chemotherapy 56(8): 4478-4482.

97. Hurdle JG, O'Neill AJ, Chopra I, Lee RE (2011) Targeting bacterial membrane function: an underexploited mechanism for treating persistent infections. Nature Reviews Microbiology 9(1): 62-75.

98. Yang ST, Shin SY, Lee CW, Kim YC, Hahm KS, et al. (2003) Selective cytotoxicity following Arg-to-Lys substitution in tritrpticin adopting a unique amphipathic turn structure. FEBS letters 540(1-3): 229-233.

99. Navarre WW, Schneewind O (1999) "Surface proteins of gram-positive bacteria and mechanisms of their targeting to the cell wall envelope". Microbiology and Molecular Biology Reviews 63(1): 174- 229.

100. Kovaliov M, Zats GM, Albeck A, Gellerman G Shatzmiller S (2017)" Why Gram-Positive Bacteria are Easier to Eradicate with the N-CH3Analogs?"; BAOJ Neurol 3(5): 1-7.

101. Malanovic N, Lohner K (2016) Gram-positive bacterial cell envelopes: The impact on the activity of antimicrobial peptides. BiochimicaetBiophysica Acta (BBA)-Biomembranes 1858(5): 936-946.

102. Wang G (2014) "Human antimicrobial peptides and proteins". Pharmaceuticals 7(5): 545-594.

103. Trias J, Nikaido H (1990) "Protein D2 channel of the Pseudomonas aeruginosa outer membrane has a binding site for basic amino acids and peptides". Journal of Biological Chemistry 265(26): 15680-15684.

104. Bechara C, Sagan S (2013) "Cell-penetrating peptides: 20 years later, where do we stand?" FEBS Letters 587(12): 1693-1702.

105. Stites WE (1997) "Protein-Protein Interactions: Interface Structure, Binding Thermodynamics, and Mutational Analysis". Chemical Reviews 97(5): 1233-1250.