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To the investigating pesticides for antibiotics of the future

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Abstract

As bacteria develop resistance to antibiotics, human health is put at risk due to factors such as inadequate treatment duration, incorrect dosage intervals, and negligible doses. The development of antibiotic resistance has been a major problem in recent years, but antimicrobials produced from medicinal plants provide a potential new weapon in the fight against infectious diseases. Peptides are present in the cells of all organisms. Antibiotics, enzymes that neutralize infections, and hormones that regulate development in several domains, including sexual maturation and growth, are among their numerous functions. Importantly, peptide-mediated innate immunity serves as the host's first defensive mechanism. The vast majority of these genetically encoded peptides swiftly eliminate a wide range of microbes after the onset of a microbial infection.

Keywords: Pesticides, Antibiotics, Bacteria, Health and Antimicrobials

Introduction

The scientific discipline known as biology is concerned with the study of all forms of life. The five pillars of contemporary biology are the study of cells, genetics, evolution, homeostasis, and energy. A common theory proposes that cells are the fundamental building block of all forms of life. There is a cell at the core of every living creature. Natural selection, according to evolution theory, causes all forms of life to branch out from a common ancestor. Inheritance in all living things begins with genes. When interconnected regulatory systems allow a cell to keep its internal environment relatively constant, this process is known as homeostasis. Having a constant supply of energy is crucial for every living thing to stay alive. By probing biological networks using suitable peptides and peptidomimetics, this thesis aims to shed light on the complicated biological phenomena.

In the medical field, the increasing prevalence of bacteria that are able to withstand antibiotics is a major challenge. The health of patients might suffer as a result of the inappropriate administration of antibiotics, such as using too little medication, not treating for long enough, or taking antibiotics at the wrong intervals. Genetic mutations, resistance to antibiotics (through mechanisms such as decreased uptake and efflux), the creation antibiotic-degrading enzymes: and impaired binding of administered medications to the areas where they are most effective. Natural medicines, such as secondary metabolites from plants, produce less side effects compared to synthetic antibiotics.

An important factor contributing to this is the idea of evolution via natural selection. Everything in the natural world is always changing as creatures adapt to their surroundings. This phenomenon also applies to microbes. Antimicrobial resistance may manifest in several ways, including changes to the medicinal site, preventing efflux transport, or modifying pathways involved in growth metabolism. Among the most prevalent antibiotics, almost 70% of infectious bacteria have evolved resistance. A major contributor to the development of pathogenic microbes that are able to withstand antibiotic activity is the long-term use of these drugs, as has been extensively shown in the

literature. Knowing how antimicrobials target microorganisms is crucial for understanding acquired antimicrobial resistance and possible solutions to this problem.

There are primarily two categories into which antibacterial agents fall: bacteriostatic and bactericidal. Bactericidal drugs may kill microorganisms independently of the human immune system, in contrast to bacteriostatic therapies that only stop the growth and replication of their target microbes. Different antibiotics work by targeting certain bacterial cell types. Inhibitors of cell wall synthesis include bactericidal penicillin, carbapenems, bacteriostatic tetracyclines, and bactericidal quinolones. Inhibitors of DNA replication include bactericidal quinolones, and macrolides and bacteriostatic sulfonamides both inhibit protein synthesis and act as competing inhibitors.

Literature Review

According to Basu *et al*., [2021] [1], vasicine is mostly produced by A. *vasica*. For over two millennia, people have turned to this herb for relief from respiratory problems. The microbial growth inhibitory activity on *Staphylococcus aureus*, *Candida albicans*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Staphylococcus pneumoniae*, *Escherichia coli*, *Pseudomonas aureus*, Acinetobacter flovus, and *Cryptococcus neoformans* was assessed by applying a vasicine-based methanolic leaf extract of *Justicia adhatoda*. There were alkaloids detected in the extracts. Among fungi, A. flavus had the lowest minimum inhibitory concentration (MIC), while C. *neoformans* and C. *albicans* had the highest. In bacteria, S. *marcescens*, At the lowest MIC were P. *aeruginosa* and E. *coli*, while the largest inhibitory effect was shown by S. *aureus*, S. *pneumoniae*, and K. pneumoniae.

Jan *et al*., [2022] [3], The effectiveness of 33 plant ethanolic extracts against P. *aeruginosa*, E. *Staphylococcus aureus*, Salmonella typhi, *Proteus vulgaris*, and E. *coli* were the microorganisms examined. Researchers looked for evidence of strong antibacterial activity in the extracts. The *Cedrella serrate*, *Ajuga bracteosa*, *Mentha viridis*, and *Juglans regia* ethanol extracts. They came to the conclusion that the plants may be used medicinally and to cure illnesses.

The antimicrobial activity of Acalypha indica leaf extracts was investigated by Rajaselvam *et al*., [2022] [4] using agar well diffusion testing for Salmonella, *Escherichia coli*, *Bacillus subtilis*, Klebsiella, and *Staphylococcus aureus*. The acetone extract showed the greatest efficacy against *Staphylococcus aureus* and B. *subtilis*, but the Among several bacteria, the aqueous extract exhibited the widest zone of inhibition against *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*. Shown reluctance to water-based solution by *Klebsiella* sp.

Sharmaand Singh [2022] [5] As mentioned in the Charaka Samhita, the plant Holoptelea integrifolia is used in the management of a variety of medical conditions. Some examples of these symptoms include acid gastritis, flatulence, worms in the intestines, vomiting, sores, vitiligo, filariasis, dysmenorrhea, and rheumatism. There have been several reports of the plants' therapeutic properties among the labourers.

Stanley *et al*. [2014] [6] examined the effectiveness of *Chromolaena odorata* as an antibacterial agent against two human illnesses, namely Proteus mirabilis with *Staphylococcus aureus*. In a study conducted by Gauniyal and Teotia [2014] [7], an ethanolic extract of leaves was shown to have an antibacterial effect against several oral infection pathogens. The minimum inhibitory concentration (MIC) for S. aureus was 0.25 mg/ml and for E. *coli* it was 0.125 mg/ml. Two common bacteria, *Streptococcus species* mutans and *Enterococcus faecalis*, were not inhibited in their spread by edible fractions of *Cinnamum zeylanicum*, Aloe barbadensis, and *Tinospora coridfolia*. Extracts from *Curcuma longa*, *Allium sativum*, *Ocimum sanctum*, *Glycyrrhiza glabra*, and *Piper nigrum* were shown to be effective against E. *faecalis*, S. *mutans*, *Candida albicans*, *Candida tropicalis*, and *Lactobacillus acidophilus* in an ethanolic test. shown promising antibacterial action. Their research led them to the conclusion that these plants had antibacterial properties that might be useful in many applications.

Peptides

Peptides are small protein segments that typically include between two and fifty protein building blocks. *Amino acids* are the building blocks of proteins and peptides. All living things have peptides in their cells. Among their many roles, they produce antibiotics, enzymes that neutralize pathogens, and hormones that control development in many areas, including growth and sexual maturation. Life could not exist if peptides did not exist. When compared to protein, peptides are much more convenient in the lab in terms of synthesis, storage, cost, and handling. Chemical biologists have been exploring peptides as a model system for studying protein function, potential vaccine candidates, and regulatory domains in artificial transcription factors over the last several decades.

Peptide vaccine

The advantages of peptide vaccines over traditional DNA and protein vaccines are their cheap cost, ease of handling, and relative safety. A TH-epitope and an epitope that generates a particular antibody or cytotoxic T lymphocyte (CTL) response are the two essential features that synthetic peptides must include in order to have an effective immune response. In order to induce antibodies, synthetic peptide-based vaccinations typically have at least 10 residues. The secretion of sperm by men and the release of eggs by females are regulated by luteinizing hormone releasing hormone (LHRH). Inducing a robust antibody response and effectively preventing conception in female mice was shown to be possible using a linear synthetic peptide that combined a TH-epitope with the N-terminal 10 residues of the hormone.

Peptide based regulatory domain

Typically, transcription factors found in nature include both a domain that binds DNA and another domain that does regulatory work. The regulatory domain may connect to its corresponding DNA sequence and interact with other regulatory proteins or RNA polymerase. A DBD is also present. An artificial transcription factor's (ATF) regulatory domain may activate or inhibit transcription. The majority of ATFs with activation domains (AD) come from peptide sequences that have their roots in naturally occurring ADs.

While most ADs found in nature are unstructured peptides, they may fold into amphipathic helices if given the chance.

Peptidomimetics

Peptides that imitate their partner proteins may be able to compensate for the low target specificity of small molecule medicines. Yet, there are a number of restrictions on peptide medication use. (a) Peptides have a number of drawbacks when it comes to oral delivery: they are easily broken down by enzymes, which makes them ineffective; (b) their hydrophilicity makes them resistant to the blood-brain barrier; (c) the kidneys and liver help get rid of them quickly; and (d) peptides can take on multiple forms, some of which interact with the target and others with unwanted receptors, making them more likely to cause side effects. Proteometics and restricted peptides might help with a some of the problems mentioned before. Peptidomimetics are chemicals that mimic the effects of a real peptide or protein. Two of the primary ways to get around peptides' inherent characteristics-their high selectivity and resistance to proteolysis-are goals of peptididomimetics. That is why peptidomimetics are so promising for use in the pharmaceutical industry.

Helix mimetics

The protein-protein and protein-nucleic complex crystal structures often reveal distinct secondary structures, such as helix or hairpin, on the protein's interaction face. One or more α helical Many interactions between proteins and between proteins and nucleic acids include motifs that are crucial for maintaining intricate patterns of gene regulation. Comparatively, protein binding domains (DBDs) are easier to mimic than transcription factor DBDs.

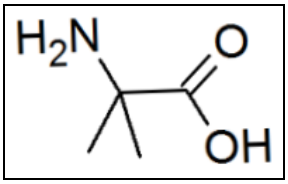

Fig 1: Chemical structure of α amino isobutyric acid (Aib)

Turn mimetics

In proteins, the β structure is another significant secondary structure. The most common kinds of β structures are the β turn and higher-order β structures like the β sheet and the β barrel. In order to connect two extended lengths of chain with opposing orientations, the most energetically advantageous polypeptide architecture is β twists. The result is the creation of βhairpin, a structural element that may be used as a module in longer antiparallel βsheets. Through βturns, several proteins and peptides engage in interaction. The side chains of βturns are perfect for molecular mimicking protein surface recognition sites and drug design targets, and βturns offer topological advantages. Imposing a semirigid hairpin stabilising template onto a known-structure proteins are among the most direct methods to imitate hairpins.

Antimicrobial Peptides (AMPS)

Across the entire evolutionary tree, AMPs are present in almost every known form of life. All multicellular creatures are "born with" the ability to fight against harmful bacteria, and AMPs are the key components of this defense mechanism. As the first line of defense for the host, peptide-mediated innate immunity is crucial. The majority of these peptides encoded by genes are activated soon after a microbial infection has taken place and quickly kill a variety of microorganisms. AMPs were first isolated from insect lymph, frog skin, and neutrophils in mammals about 30 years ago. Ever since then, a plethora of cationic peptides have been documented from a wide range of animals, extracted from many tissues and organs, including as the respiratory and gastrointestinal tracts, the oral mucosa, the pancreas, and the eyes. Mammals primarily produce two types of AMPs: defensins and cathelicidins.

Selectivity

Distinct microenvironmental factors and basic distinctions between microbial and mammalian host cells account for the selectivity of antimicrobial peptides. Various zwitterionic components, including sphingomyelin (SM), cholesterol, ergosterol, and phosphatidylcholine (PC) are found in eukaryotic membranes. Alternatively, phosphatidylserine (PS), cardiolipin (CL), and hydroxylated phospholipids (PG) make up the bulk of negatively charged components in prokaryotic design. The peptides reach the other side of the cell membrane by means of hydrophobic interactions, which set in motion the interaction between the AMPs' positive charges and the phospholipids' negative charges seen in bacteria.

Mode of Action

It is believed that AMPs do not cause resistance because their method of action is nonspecific, in contrast to conventional antibiotics, which are often targeted at a specific cellular receptor. There are many different theories on how AMPs exert their lytic activity, and a great deal of significance about this topic have no clear answers. Due to the anionic nature of most bacterial surfaces, the first point of contact between the AMPs and the target microbe's outer leaflet would be electrostatic. When approaching bio membranes, the linear AMPs reorganize and take on an ideal amphipathic shape. Phospholipid head groups are interacted with by the hydrophilic face, whereas the hydrophobic face is introduced into the bilayer core. The structural deformation of the membrane architecture might occur via several processes as a result of these interactions. Three models: the toroidal pore, the barrel-stave, and the carpet are three descriptions of how membrane-active peptides enter microbial membranes. Here are the specifics of these models:

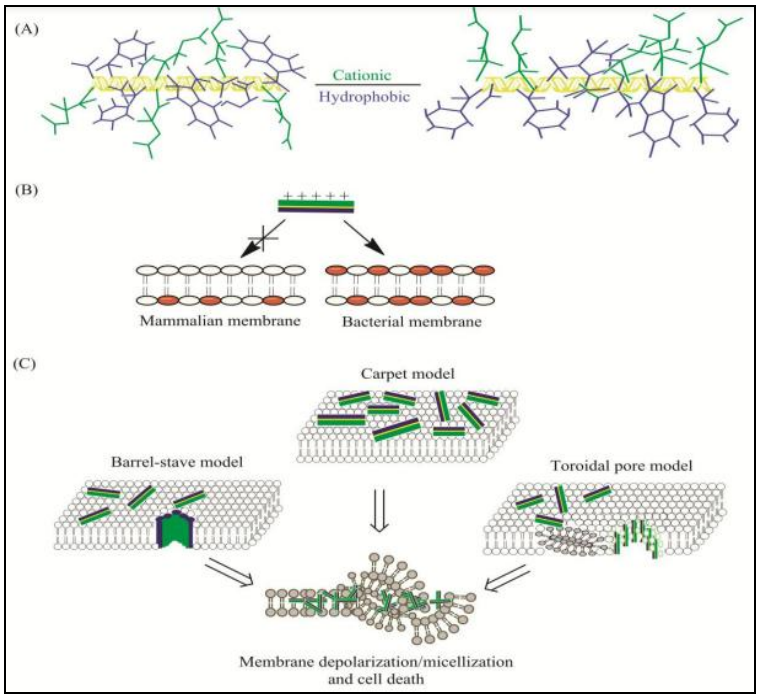

Fig 2: Diagram depicting the process by which AMPs cause the permeabilization and disruption of bacterial membranes. (A) When AMPs are near a biological membrane, they take on an amphiphatic shape. (B) Electric field representation of AMPs' bacterial selectivity relative to mammalian cell viability. In (C), we provide models for membrane permeabilization.

Resistance to AMPs

A phenotypic that includes the level of AMP resistance in a given pathogen is predicated on the assumption that most bacteria possess distinct inherent susceptibilities to these defense chemicals. Constructive mechanisms are the natural processes that lead to resistance development to amps. It is becoming more and more apparent that AMP resistance is a distinguishing trait of some significant human diseases, even whereas microbes' ability to resist AMP destruction seems to represent a significant barrier development. Some bacterial species have developed mechanisms that make them resistant to AMPs. Some bacteria, such as Serratia, Proteus, Providencia, and Pseudomonas, have a unique membrane composition that makes them naturally resistant to AMPs. As an additional defense mechanism against AMP-induced stress, bacteria have evolved an inducible method of resistance.

Therapeutic potential of AMPs

Due to their broad antibacterial spectrum and capacity to fight against bacteria and pathogens that have developed a tolerance for other drugs, AMPs are an exciting new category of therapeutic agents more traditional antibiotics. Additionally, AMPs may enhance traditional antibiotic treatment, likely via a synergistic action that allows antibiotics to enter bacterial cells more easily. By attracting antigen-presenting cells, decreasing Pro-inflammatory cytokine production produced by lipopolysaccharide (LPS) and/or functioning as chemokines, AMPs may start adaptive immune responses. When AMPs are engaged in infection clearance, such as wound healing promotion, they may also have immunomodulatory function. These characteristics led to the suggestion of the name "host defense peptides" for AMPs, which better describes their function in their target bioenvironment.

Lipopeptides

In addition to ribosomal antimicrobial agents, bacteria and fungi may create lipopeptides when grown on different carbon sources. Aliphatic acids link the N-terminus of six or seven amino acids to brief cationic or anionic peptidic groups, making up their moiety. The cyclic structures of natural lipopeptides are often rather complicated. Some of them cause cell membrane disruption via unknown methods, which is how they exert their lytic effect. To kill bacteria, cationic lipopeptides work in the same way that amphibian polysaccharides (AMPs) do: by electrostatically interacting with microorganisms that are Gram-negative or Gram-positive, as well as their lipopolysaccharide (LPS) or lipoteichoic acid, which are negatively charged.

Short Lipopeptides: According to many studies, one promising strategy for developing effective antibacterial medicines is to link an aliphatic chain of an appropriate length the end of natural or synthetic short peptides, thereby simulating the action of natural lipopeptide antibiotics. Previous research by Shai *et al*. shown that the powerful native antibacterial peptide magainin gained antifungal action upon fatty acid conjugation. To further investigate [D]-4-magainin and [D]-L6K6, two diastereomeric lytic peptides, were chosen by Shai *et al*. to investigate whether an antibacterial peptide scaffold is required for the antifungal action of these conjugate compounds. Short aliphatic tail lipopeptides (ten to twelve carbon atoms) were shown to be efficient against both bacteria and fungus without causing haemolysis. Conversely, effective antifungal medicines are lipopeptides with long aliphatic tails (14 or 16 carbon atoms). Exceeding their MIC values is the only concentration at which they cause haemolysis. In order to create fatty acid conjugates, diastereomers are preferable than every peptide containing a L-amino acid.

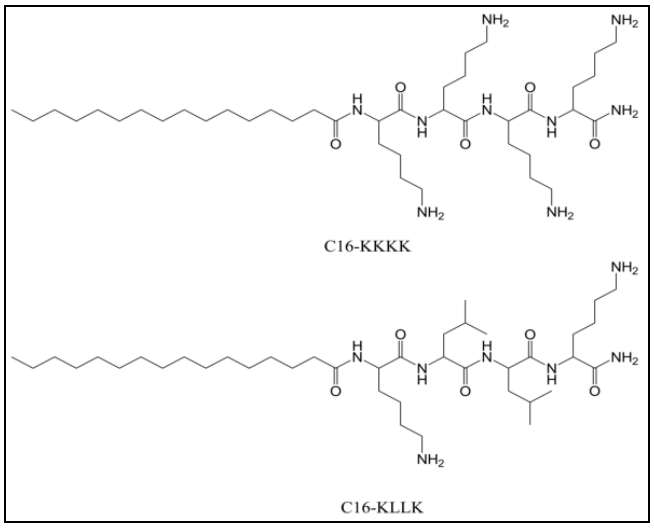

Fig 3: The molecular blueprint of the C16-KKKK and C16-KLLK short lipopeptides

Small cationic peptidomimetics

Several groups of researchers have studied the minimal *Cationic antimicrobial* peptide pharmacophore: charge, lipophilicity/bulk in the last ten years. With this, peptide-based antibiotic research may go in a new path, and there's a chance that short, inexpensive antimicrobial peptidomimetics can be developed for systemic usage. The bactericidal efficacy of natural peptide scaffolds was investigated by using a partial 15-residue bovine lactoferricin (LFB) molecule. Substituting another hydrophobic natural amino acid, such as phenylalanine, for either of the two tryptophan (Trp) residues in this shortened sequence rendered it completely inactive against bacteria. According to another investigation, the antibacterial activity of lactoferricins from humans, goats, and pigs may be increased by a factor of up to six when an additional Trp is introduced.

Using the fluorine analogue fF and the trifluoromethyl substituted phenylalanine analogue tfF, the effect of fluorine's hydrophobicity was studied by Gime'nez *et al*. Antibacterial activity was shown, for instance, by peptide scaffolds SCAMP-I and SCAMP-II that had the same number of tryptophan residues as those containing fluorinated phenylalanine (Figure 4) similar to that of the latter. These results indicate that the hydrophobic bulk of phenylalanine residues replaced with fluorine is almost the same as that of tryptophan. At 250 µg/mL, it was shown that none of the synthesized peptide molecules containing fluorinated amino acids were haemolytic.

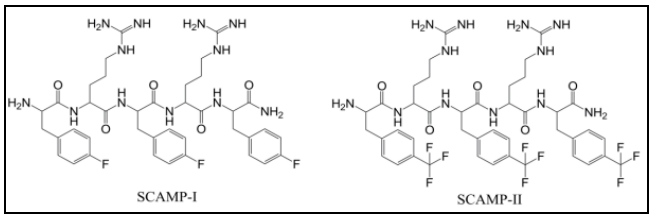

Fig 4: Structure of SCAMP-I and SCAMP-II chemically

In a similar vein, Sharma *et al*. attempted to replace native histidine amino acid residue with derivatives that had an aliphatic group replaced for it.

Conclusion

The phytochemical components found in plant extracts have a wide variety of medical applications, one of which is an antibacterial impact. The major objective of the study was to analyze the phytochemical makeup of plant extracts in order to discover and evaluate their antibacterial activity against antibiotic-resistant pathogens. Vaccinations based on synthetic peptides usually have at least 10 residues to generate antibodies. Some of the issues previously described could be alleviated by proteome tics and limited peptides. The development of antibiotic resistance has been a major problem in recent years, but antimicrobials produced from medicinal plants provide a potential new weapon in the fight against infectious diseases. Peptides are present in the cells of all organisms.

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