Review Article

Title: "Natural Antimicrobial Peptides: An emerging therapeutic agent against pathogens"

Abstract

The pace of discovery of new antibiotics is far slower than the emergence of antibiotic-resistant strains in the environment. This global problem is more acute in developing countries. Therefore, we need to develop some alternative approaches to combat infections caused by potent antimicrobial agents that are isolated from different sources like plants, animals, humans, bacteria, and fungi. These antimicrobial peptides may have a ribosomal or non-ribosomal origin. Natural antimicrobial peptides have diverse functions such as in agriculture, pharmaceutical industries, beverages, food industries, and medicine. NAMPs have been used as food preservatives against food-borne pathogens and to increase the shelf-life of the food items which is increasing demand of consumers now-a-days. They are also used for the treatment of peptic ulcers, wound healing, various infections caused by microorganisms. Different types of natural antimicrobial peptides are universal in nature and show broad-spectrum antimicrobial activities. NAMPs exhibit great potency against multidrug-resistant bacteria e.g., methicillin-resistant *Staphylococcus aureus* (MRSA). NAMPs have unique characteristics of targeting multiple pathogenic strains and prevent the emergence of natural resistance. In this review article, we have systematically discussed different types of natural antimicrobial peptides, their classification, expression, diversity and source of origin. We have also explored their mode of action, genetic regulation and application as an alternative therapeutic agent.

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Keywords: Natural antimicrobial peptides, Animal peptides, Plants peptide, Lantibiotics, Alternative therapeutic agent.

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Introduction

Natural antimicrobial peptides (NAMPs) are promising antimicrobial agents because of natural origin that creates less selection pressure on the microbes and prevent the emergence of resistant strains compared to chemically synthesized antimicrobials. NAMPs are family of small polypeptides that are produced by a microorganism and show broad-spectrum anti-bacterial, anti- fungi, anti-viral and anti-parasitic activity and termed as next-generation antibiotics. Due to their broad-spectrum therapeutic effects, low toxicity and the low rates of mutations in pathogenic bacteria [1]. There are several natural antimicrobial agents isolated from the soil, plants, animals, and microbes such as Bacteriocins, Lantibiotics, Nisin, and Natamycin. Bacteriocins are antimicrobial substances produced by lactic acid bacteria (LAB) including organic acids, hydrogen peroxide, diacetyl, and inhibitory enzymes. Bacteriocins are proteinaceous compounds that kill closely related bacteria with a bactericidal mode of action. Nisin is the first antimicrobial agent that was discovered before penicillin and has been popularly used as a safe replacement for chemical reagents in food preservation for over 50 years. Lantibiotics are one of the most promising candidates for future antibiotics. Till now, more than 200 Lantibiotics have been isolated, identified, and characterized. However, only Nisin got the FDA approval for the use as an antimicrobial agent until now [2]. One possible reason is that any antimicrobial agent has to pass through the stringent toxicity testing before approval by the authorities.

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It is to be noted that all the antimicrobial agents isolated from microbes are from culturable bacterial strains. As we know, only less than 1% of the bacterial population is culturable and more than 99% of the bacterial strains remain in viable but not culturable (VBNC) state in the environmental samples. These strains cannot be cultured in the laboratory by routine culture methods and have been ignored by the scientist. Therefore, we need to develop some advanced methods to isolate natural antimicrobial agents (NAMs) from environmental samples. Advancement of genomics has open new ways to isolate NAMs from the VBNC population of bacteria too. One possible method is to use functional metagenomics to identify natural antimicrobials from the environmental samples because it does not require the purification of culture. In functional genomics, we directly isolate the DNA from the environmental samples and make libraries of the DNA fragments and do the functional assay in a heterologous host. This allows the identification of NAMs from the culturable and non-culturable bacterial population. The purpose of this review article is to recapitulate the recent developments in the field of natural antimicrobial peptides research, concisely, the types of NAMPs, their classification, mode of action, genetic regulation, potential applications, and future perspectives.

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Historical perspective of NAMPs

Alexander Fleming in the late 1920s identified lysozyme and considered it as the first antimicrobial peptide [3], the exact mode of action of lysozyme was not known until 1958 when Salton discovered that lysozyme degrades the bacterial cell wall [4]. Antimicrobial peptides were first noted in prokaryotic cells. [5] isolated an antimicrobial substance from *Bacillus brevis* and named as gramicidin, which showed in vitro and in vivo activity against many Gram-positive bacteria. Later, it was announced that Gramicidin is beneficial against infected wounds of

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guinea-pig and used as a therapeutic agent [6]. In 1941, antimicrobial peptide Tyrocidine was reported with activity against both Gram-positive and Gram-negative bacteria [7]. In 1942, the antimicrobial peptide-like substance was isolated from the endosperm of wheat (*Triticum aestivum*) which exhibits antimicrobial activity against various phytopathogens such as *Pseudomonas solanacearum, Xanthomonas compestris* [8]. Later on, it was named as purothionin [9,10]. In 1956, antimicrobial peptide defensin was isolated from the leukocyte of rabbit [10]. The antimicrobial protein lactoferrin was obtained from milk [11,12]. In 1987, antimicrobial agent magainins were isolated from the African clawed frog *Xenopus laevis*. In 1990, the first anionic antimicrobial peptide was isolated from Xenopus laevis [13]. Hiolbiotics, colicin, lantibiotic, and microcin are identified as prokaryotic peptides [14].

Bacterial NAMPs

Several Gram-positive and Gram-negative bacteria produce and secrete cationic or neutral antimicrobial peptides. The bacterial NAMPs are also termed as peptide bacteriocins (Table 1) [15]. Bacteriocins are lethal to bacteria other than the producing strain and are classified largely based on differences in their molecular weight. The common mechanism of action of antimicrobial peptides with the bacterial origin is by permeabilization of the target cell membranes [16,17]. Some peptide bacteriocins have specific mechanisms that inhibit bacterial metabolic functions. For example, peptide microcin C7 inhibits protein synthesis and peptide mersacidin inhibits peptidoglycan biosynthesis.

One of the most important natural antimicrobial peptides is lantibiotic which has antimicrobial activity against Gram-positive pathogens including many antibiotic-resistant bacteria. Lantibiotics are recognized by the presence of lanthionine or methyl-lanthionine amino

acid formed with the help of intramolecular cross-linking of cysteine thiols to dehydrated serine and threonine residues [18]. They can be used as food preservatives, additives, probiotics, and preventive medicine. Lantibiotics are made up of lanthionine-containing antibiotics and they are incorporated on the ribosome as a pre-peptide which undergoes substantial post-translational modification to form a biologically active peptide. Lantibiotics are synthesized by most Gram-positive bacteria and few Gram-negative bacteria [19]. They reveal antimicrobial activity predominantly against Gram-positive bacteria by the formation of spore in the cell membrane [20].

Nisin is the first most promising lantibiotic which was discovered in 1920 and used as a food preservative in food industries [21]. They show the antimicrobial activity predominantly against Gram-positive bacteria by spore formation inside the cell membrane. The peptide Nisin is produced by *Lactococcus lactis*. Natamycin is also used for food preservation against the food spoilage organisms particularly yeast or molds. Natamycin is powerful against around all molds and yeasts. It is isolated from *Streptomyces natalensis*. It has been observed that natamycin has little or no activity against many pathogenic bacteria. Due to its antifungal nature, it has been used in various products like dairy, meats and other animal food items. Reuterin is an antimicrobial compound produced by *Lacotobacillus reuteri*. It is water-soluble non-proteinaceous with broad antimicrobial activity. It is effective against Gram-negative and Gram-positive bacteria, filamentous (molds), and nonfilamentous (yeasts) fungi [22]. Reuterin show bacteriostatic activity particularly against *Listeria monocytogenes* and many pathogenic bacteria.

Plant NAMPs

Plants produce antimicrobial peptides as a part of their defense mechanisms against pathogens. They primarily target pathogenic fungi, however, antibacterial and insecticidal activities are also reported [34]. Fungicidal mechanisms of most of these peptides remain to be investigated [35]. Defensins, thionins, lipid transfer proteins, hevein-like peptides are plant producing antimicrobial peptides. Plant defensins are small, highly stable, cysteine-rich peptides with antifungal properties [36]. They are progressive against Fusarium spp., *Saccharomyces cerevisiae*, and *C. Albicans* [37]. Eugenol is a volatile phenolic compound and is the major constituent (70–90%) of cloves which is responsible for the aroma of clove. It is extracted from clove buds and leaves which plays a prominent role in dental and oral hygiene. Eugenol is used as flavor, irritant, sensitizer and can be used as local anesthesia. Eugenol has been used in the formation of dental materials in clinical dentistry and is very effective against Salmonella, Shigella, *Clostridium botulinum*, *Listeria monocytogenes* and *E. coli* [38]. Thionins are one of the major groups of plant NAMPs. α-purothionin is the first thionin which is isolated from wheat endosperm. These plant NAMPs are known as plant toxins with antifungal and antibacterial activity. Expressions of thionins in plant tissues could be initiated by exposure to different pathogens [39]. Hevein-like peptides are first synthesized from *Hevea brasiliensis*. Due to their high glycine content and conservative lectin domains, they have high bonding ability to the chitin layer of the chitin-containing fungi, therefore inhibiting their growth [40].

Animal NAMPs

NAMPs obtained from mammals, amphibians, and fish, etc. are termed as animal peptides. Antimicrobial peptides the mucosal epithelial cells and Paneth cells both are secreted from

mammals. Mammalian leukocytes are a rich source of antimicrobial peptides that help in prevention against bacterial infections. These antimicrobial peptides are cationic in nature [41]. Protamine and Pleurocidin are two major types of animal antimicrobial peptides which is synthesized from fish which showed activity against *L. monocytogenes* and other food-spoiling microorganisms hence may be used in food preservation. Lactoperoxidase enzyme (LP) belongs to the peroxidase family and its primary function is to catalyze the oxidation of molecules. Lactoperoxidase is a group of natural enzymes, generally dispersed in nature and form in many animals and plants, ductal epithelial cells of mammary gland secreted human Lactoperoxidase (LP). In bovine milk the level of (LP)is about 20 times higher than human milk and changes continually during the postpartum periods. Lactoperoxidase enzyme is very effective against Salmonellae, Shigella, Pseudomonas and coliforms. [42]. Thiocyanate, which is present in saliva, milk, and airways is a potent antimicrobial activity. Avidin is a positively charged glycoprotein that is present in eggs. Egg also contains biotin. Avidin binds biotin (avidin-biotin system is used as a diagnostic tool in immunoassays) and makes biotin unavailable for the use of microorganisms. Avidin can effectively inhibit the growth of *E. coli, Klebsiella pneumoniae*, *Serratia marcescens*, and *P. aeruginosa*. [43]. Protamine used as a natural food preservative .it is cationic antimicrobial peptides and It is obtained from fishes. Protamine show high stability under heat and it is used for food application as a preservative in food packaging. Protamine does not influence the sensorial characteristics (texture, smell, or taste) of the food item to which it is added [44]. It is effective against Gram-positive and Gram-negative bacteria and also yeast and molds [45].

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Classification and diversity of NAMPs

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There are different types of natural antimicrobial peptides found in nature. Natural antimicrobial peptides are classified on the basis of structures, origins, and mode of action:

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Classification on the basis of structure

NAMPs are commonly classified based on their secondary structure i.e. α-helical, β-sheet, or peptides with random-coil structure [46,47,48]. Most of the NAMPs belong to the first two categories. α-helical peptides are generally unstructured in solvent, and accept amphipathic helical structure when it comes in approach with a biological membrane [49,48]. Two of the most studied peptides in this group are (i) LL-37 [48, 50]. which is produced as an inactive precursor in the antimicrobial protein (hCAP18; human cathelicidin) present in neutrophils and epithelial cells [51] (ii) human lactoferricin which is derived by proteolytic cleavage of the antimicrobial and immunomodulatory iron-binding glycoprotein lactoferrin present in milk and exocrine secretions [52,53]. β-sheet peptides are stabilized by disulfide bonds [54,55] and are organized to create an amphipathic molecule [49]. The β-sheet peptides are more ordered in aqueous solution due to their rigid structure and do not undergo drastic conformational changes compared to helical peptides upon membrane interaction [49]. The best-studied β-sheet peptides are the defensins that are produced as inactive precursors in neutrophils, macrophages, and epithelial cells [51,48].

Most NAMPs have a common structure where domains of hydrophobic and cationic amino acids are spatially arranged into an amphipathic design which facilitates their interaction with bacterial membranes [56- 58]. These peptides revealed important structural hallmarks of this novel antibiotics. Defensin family peptides range from almost 20-30 amino acid in length and are describe by 6 sustain cysteine residues and intramolecular disulfide bond formation and

these peptides can yield to an amphipathic α-helical structure in hydrophobic conditions. This conformation enables the insertion of the peptide into the cell membrane, resulting in membrane destabilization and microbial lysis [59- 61]. Some natural NAMPs belong to the third class of random-coil peptides which lack secondary structure and often contain a high content of arginine, proline, tryptophan, and/or histidine residues [46, 47]. Similar to other NAMPs, many of the extended peptides fold into amphipathic structures after contact with a membrane [47]. One of the most effective peptides in this group is indolicidin and it originates from bovine leukocytes [54].

Classification on the basis of Origin

Natural antimicrobial peptides are classified on the basis of origin from different sources. NAMPs vary substantially even among mammalian species. Defensin is very useful molecules and which is characterized via keratinocyte cells and its play an important role in innate immune system mostly in skin and liver. They are cationic sequences, rich in cysteines, which enable them to form disulfide bridges and stabilize themselves by the conformation they generally adopt of the beta-leaf type [62], studies show that these molecules interact with the microorganism through electrostatic interactions with the lipid membrane of the host generating pores, promoting the death of the microbe by osmotic imbalance [63]. Human beta-defensin type 2 (hBD-2) is very useful as a pro-inflammatory molecule in psoriasis and acne lesion stimulate by the existence of *P. acne* bacteria [64]. The bactenecins (Bac5 and 7) was the first mammalian cathelicidin which were isolated from bovine neutrophils and rabbit CAP18 from granulocytes. Although multiple cathelicidins are present in cattle, buffalo, horse, chicken, and fish.In human, primates,mice and rat only a single gene for cathelicidin has been found. The multiple genes present in castles could be the result of selective pressure for disease resistance

from the domestication of these animals [65]. Cathelicidins are expressed by different epithelial cells such as keratinocytes, mast cells, neutrophils [66]. It collaborates at the beginning by electrostatic action with the membrane of the *P. acnes* and it has been demonstrated that due to its tertiary structure it is capable of being inserted in the lipid bi-layer promoting the formation of pores-channel that allow the entry and exit of cellular material, resulting in the death of the pathogen [67,68].

Lactoferrin (LF) is an iron-binding glycoprotein that is part of the innate defense system. Lactoferrin also has antibacterial, antiviral, antiparasitic, catalytic, anti-cancer, and anti-allergic functions and properties [69]. The LF can bind and trap Fe3+ ion and interact with the bacterial membrane directly, resulting in the antibacterial activity [70,71,72]. The synthetic hLF1-11 peptide is a lactoferrin derivative corresponding to the N-terminal eleven residues of human lactoferrin. The hLF1-11 peptide shows antimicrobial activity against both Gram-positive and Gram-negative bacteria and various fungi. The synthetic peptide is also effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Acinetobacter baumannii* strains [73- 75]. hLF1-11 is used with standard antibiotic for a synergistic effect and hLF1-11 is active against fluconazole resistant candida albicans. Preincubation of fluconazole-resistant *C. albicans* with hLF1-11 significantly enhances the candidacidal effect of fluconazole [76].

Thionins are one of the major groups of plant NAMPs. Expression of thionins in plant tissues could be triggered by exposure to various pathogens [39]. Their anti-infective mechanism of action is demonstrated by the interaction between thionins hydrophobic residues and the positively charged membranes of pathogens. The proposed mechanism associated to the lysis of cell membranes but it appearance under analysis. Another proposed antimicrobial activity is disrupting the calcium influx during the cellular activity which changes the membrane polarity [77]. Berocall-Lobo et al. (2009) showed that wheat thionin, antibacterial activity against

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Leishmania donovani was highest among plant NAMPs. They collapsed calcium channels and pH gradients across the parasite plasma membrane together with a rapid depletion of intracellular ATP without affecting mitochondrial potential. Hence, the lethal effect of thionins was mostly associated with permeabilization of the plasma membrane leading to immediate death of the parasite. Thionins are mostly found in seeds and act as a defense molecule against ingesting by animals. A highly toxic to plant pathogens thionin isolated from barley (Hordeum vulgare) leaf is involved in the mechanism of plant defense against microbial infections [78]. The hydrophobic protein crambin from the Abyssinian kale (*Crambe abyssinica*) is also a member of the thionin family [39]. Some thionins have cytotoxic activity and can be used in the development of new drugs against cancer [79]. Thionins obtained from cereals and Pyrularia pubera have four disulfide bonds. Other dicotyledonous thionins have three disulfide bonds. The structural feature common to all thionins is the G (gamma) fold consisting of two antiparallel α-helices that form a stem and antiparallel ß-sheets that form an arm [80]. A groove exists between the helical and ß -sheet segments. This was first isolated from *Hevea brasiliensis*. Due to their high glycine content and conservative lectin domains, they have high bonding ability to the chitin layer of the chitin-containing fungi that inhibit their growth [40].

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Mode of action and their function

Different types of natural antimicrobial peptides are found in nature and classified on the basis of mode of action and their function. The bacterial antimicrobial peptide-like lantibiotics, nisin, lacticin 481, nukacin ISK-1, mersacidin, lacticin 3147, haloduracin and LAB (Lactic acid bacteria) bacteriocins kill the target cells by making pores in the membrane, although alternative mechanisms, such as inhibition of cell wall synthesis, have also been reported [81]. Pore formation causes exposure of low molecular weight compounds (e.g. ions K^+, H^+, phosphate)

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leading to the degeneracy of the proton motive force (transmembrane electric potential and the pH gradient) that is toxic to the cells. Bacteriocin use the cell wall precursor molecules lipid II as the anchor molecules on the target cell in all bacteria the role of lipid II, these have relatively broad inhibitory bacteriocin [82]. Initial interaction between a bacteriocin and a target cell often involves attractive but nonspecific force, with a positively charged bacteriocin and negatively charged bacterial membrane surface. However, because of their narrow target spectrum and high potencies, it is believed that most bacteriocins bind specific receptors on the sensitive cells. Nisin binds lipid II by the lantibiotic ring structure in the N-Terminal part of the peptides, dominant to the formation of lethal pore that consist of both nisin and lipid II . Nisin and epidermin were the first lantibiotics shown to use lipid II as a docking molecule [83]. The mechanism of action for nisin has been characterized. Nisin binds lipid II via the lantibiotic ring structures in the N-terminal part of the peptide, leading to the formation of lethal pores that contain both nisin and lipid II [84]. In addition, nisin also inhibits target cells by blocking cell wall formation via interfering with the biosynthesis of peptidoglycan layer [85]. This mechanism is self-relent of the pore forming activity and engage the relocation of lipid II molecules into patches outside their functional location. A number of different Lantibiotics with N-terminal ring structures similar to nisin kill target cells by lipid II-mediated pore formation [86].

Viscotoxins belongs to plant thionins and are toxic against various number of cell types. They are produced from the leaves and stems of the European mistletoe (*Viscum album*). viscotoxin A3 and viscotoxin B are studied under fluorescence spectroscopy and show that high conformational stability and a similar conformation is solution and when bound to membrane. Viscotoxins induced the presence of deficiency on the surface of membranes that lead to the destabilization and disruption of the membrane bilayer [87].

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Animal producing natural antimicrobial peptide chitosan is obtained from partial deacetylation of chitin and sometimes known as deacetylated chitin. It is a natural polycationic

linear polysaccharide mainly found in shells of marine crustaceans [88]. Due to its nontoxicity, biodegradability, and low allergenicity, it has wide applications. It has antitumor, antifungal, antimicrobial and antioxidant activities [89]. chitosan is very powerful against Gram-negative bacteria like Bacteroides fragilis, cholera, Shigella dysenteriae, *E. coli*, and Vibrio. Mammalian antimicrobial peptide cecropin P1 in transgenic tobacco led to enhanced resistance to phytopathogenic bacteria *Pseudomonas syringae* pv. tabaci, *Pseudomonas marginata*, and *Erwinia carotovora* [90].

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Genetic regulation and expression of NAMPs

NAMPs fall into two categories based on their synthesis: non-ribosomally synthesized peptides and ribosomally synthesized (natural) peptides. Whereas the first group is mostly produced by bacteria, the other is produced by all organisms including bacteria [91]. NAMPs are classified into two groups based on the electrostatic charge characteristics. Positively charged peptides in large group peptide and other group consist of non-cationic peptides and it is divided into many subgroup such as aromatic peptide, anionic peptide and peptides [92]. Non-cationic peptides in comparison with the first group are uncommon. Mostly the term antimicrobial peptide only refers to cationic AMPs.

Cathelicidin expression is managed by a changes of circumstance at both the transcriptional and post-translational level.at both the transcriptional and post-translational levels. Expression of transcripts for the human cathelicidin precursor protein (hCAP18), encoded by the gene CAMP, is induced by 1,25-hydroxyvitamin D3 via the vitamin D responsive element (VDRE) and triggered independently of pro-inflammatory molecules in keratinocytes in vitro [93,94]. In mice, the cathelicidin gene for mCRAMP (Cnlp) derived from phagocytes is

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regulated by hypoxia-inducible factor 1α (HIF-1α) [95,96]. The cathelin domain acts as both an antimicrobial peptide as well as an inhibitor of protease activity [97]. the full-length precursor hCAP18, processed cathelicidin peptides show, potent broad-spectrum antimicrobial activity against pathogens. The peptide cleaved from hCAP18 was presumed to be the mature form and termed FALL-39 designated as the AMP containing 39 amino acids isolated from bone marrow [98].

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AMPs perform in innate immunity via play as direct inhibitors of microbial activity through the governance of immune cell function and recruitment and general mechanism proposed for their mode of action against pathogens. The cationic NAMP is likely attracted to the net negative charge of the membrane that exists on both Gram-positive and Gram-negative bacteria. The peptides coordinate with the bacterial membrane and embedded into the lipid bilayer and result the formation of pore or disrupting the grouping of the membrane as the peptides associate with lipid head groups of the lipid bilayer [99].This dominant to destabilization of the bacterial membrane and bacterial lysis. The AMP preferentially targets dividing over non dividing bacteria, especially at the site of cell division [100]. As regulators of immune function, cathelicidins have been shown in the composition of numerous cellular responses. The ability of dendritic cells to undergo phagocytosis was significantly enhanced in the presence of LL-37 through changes in the expression of phagocytic receptors [101]. LL-37, are found at different concentrations in different cells and tissue types and body fluids. LL-37 was first described in leukocytes and testis. The time-dependent LL-37 gene expression in maturing neutrophils has gained special interest recently [102,103]. LL-37, as well as its proprotein, were also found bound to plasma lipoproteins [104- 106]. Human beta-defensin-2 increases the level of LL-37 expression in colon and breast epithelial cells [107].

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Defensins represent a diverse family of AMPs ubiquitously expressed in mammals, including epithelial cells of the skin, gastrointestinal, reproductive, and respiratory systems [108,109,110]. Mature forms of defensins are also cationic, with positive charge ranging from +1 to +11.The length of small cationic peptides are between 28-44 amino acid and it contain 6 to 8 cysteine residues that facilitate the formation of intramolecular disulfide bridges. the molecular structure and configuration of these disulfide bridges are the foundation for the division of these NAMPs into specific subfamilies corresponding to α, β.

In humans α-Defensins are expressed characterized by three disulfide bridges between cysteine residues 1- 6, 2- 4, 3- 5. The α and β-defensins are derived from gene products believed to have evolved from an ancestral β-defensin gene [111]. Thus, it was thought that the divergence of the α and β-defensin family gave rise to the rapid evolution of the innate immune system which is designed to respond to the different microbial environments to which the host immune system was exposed. α-defensins expand to communicate antimicrobial host defense within the urogenital tracts, gastrointestinal and in addition to circulating immune cell. Human neutrophils encode genes corresponding to the four α-defensins designated as human neutrophil peptides 1- 4 (HNP-1 through 4) [112,113]. α-Defensins apply a binary function, like members of the cathelicidin family, as both a modulator of microbial pathogenesis through their innate AMP activity and host immune function. For example, the HNPs were found to upregulate the levels of both tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8) in human monocytes after exposure to Staphylococcus aureus while reducing the expression of cell-surface adhesion molecules in human umbilical endothelial cells activated by TNF-α [114].

Applications and future perspectives of NAMPs:

Natural antimicrobial peptides can be used as food preservatives, additives, probiotics, and prophylactics. Lantibiotics have a vast array of applications in the food industries, medicine, and

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health care. Nisin which has been used commercially is the only natural antimicrobial agent that is approved by the FDA. It has been used as a safe food preservative in processed dairy products, canned fruits, and vegetables [115]. Nisin in addition exhibits antimicrobial activity against food spoiling bacteria like *Listeria monocytogenes* [116]. It is applied in veterinary medicine as well for the treatment of bovine mastitis [117]. Nisin is effective against clinically relevant human pathogens like *Helicobacter pylori*, it is effective drug treatment in peptic ulcer. Actagardine and mersacidin appear a notable activity against methicillin resistant, staphylococcus aureus infection, oral decay and acne[118]. Gallidermin and Epidermin are effective against acne, eczema, folliculitis, and impetigo, thus they can be used for personal care products. Cinnamycin can be used against inflammation and viral infections and for blood pressure regulation [119]. Pep5 and Epidermin and Pep5 prohibit the attachment of coagulase-negative Staphylococci specifically S. epidermidis to silicon catheters [120]. Mutacin 1140 can prevent dental cavities. Duramycin and Ancovenin both are used for the treatment of inflammation and blood pressure regulation.

Natural antimicrobial agents from animals and plant origin are considered as an alternative to chemical preservatives because of the safety, no toxic effects, and extension of shelf life of food products [121]. Recent researches have shown the potency of bacteriophages as a preservative for food items. These can be easily propagated. It has been observed that bacteriophages are favorable because phages have the ability to target specific bacteria [122]. The antimicrobial compound obtained by *Lacotobacillus reuteri* is a water-soluble, non-proteinaceous in nature having broad antimicrobial activity. It is effective against Gram-negative, Gram-positive bacteria, filamentous (mold), and non-filamentous (yeast) fungi. It is active to a wide range of pH and resistant to various proteolytic and lipolytic enzymes [22]. It exhibits bacteriostatic activity against many pathogenic bacteria, particularly against Listeria monocytogenes. NAMPs have diverse applications and can be used as therapeutic agents

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against bacterial, fungal, and viral infections. It is very useful against some antibiotic-resistant bacteria like methicillin-resistant bacteria *S. aureus*, Vancomycin-resistant enterococcus (VRE). Some NAMPs are also used in agricultural environments like b-purothionin, cecropin B, and phor21 which exhibit antifungal activity. Alfalfa antifungal peptide synthesized from seeds of Medicago sativa, and it play very powerful activity against the unsafe fungal pathogen of potato, V. dahlia. Rice plants expressed the cecropin A gene of *Hyalophora cecropia* reveal fight resistance to *Magnaporthe grisea* the causal agent of rice blast disease. Further studies are required to extend our detailed understanding on how NAMPs function in medical settings, mode of action, toxicity, and immunogenicity. It will be crucial for the development of NAMPs into practical use in medicine as a therapeutic agent.

Natural antimicrobial peptides are very useful in humans, animals diseases, agriculture and the environment. Defensin is widely used for the preservation of the chicken and meat industry. Various bacteriocins are known to target pathogens, including *Clostridium difficile* and emerging antibiotic-resistant bacteria such as MRSA, VRE and entero-haemorrhagic *E. coli* [123- 125]. Recently, researchers have shown that bacteriocin based therapeutic approaches might be a part of the treatments against pathogens. For example, bacteriocin therapy used in distal colon models has demonstrated that the narrow-spectrum bacteriocin (sactibiotic) thuricin CD specifically eliminates *C. difficile* without disrupting the beneficial microbial community [126]. A bacteriocin placed idea might to prove good to present treatment for *C. difficile* associated intestinal diseases using a broad spectrum of antibiotic [127]. Lantibiotics (such as nisin, mersacidin and lacticin 3147) can eradicate infections caused by Strep. pneumonia and MRSA in mice [128,129] as well as having preventive effects against tooth diseases in dogs [130] and bovine mastitis in dairy cows [131]. Bacteriocin (microcin J25) isolated from gram-negative bacteria has been shown to drastically reduce Salmonella infection in a mouse model [132].

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Nisin was one of the first AMPs which was studied in an animal infection model in the early 1950s [133]. the rapid clearance of nisin A from the blood same great potency as penicillin on the treatment of *Mycobacterium tuberculosis* and *S. pyogenes* related diseases. Lysostaphin is a staphylococcin (bacteriocin) produced by *S. simulans* [134] (previously classified as class IId bacteriocin but are presently included in the group of antimicrobial proteins that enzymatically degrade bacterial cell wall) [135].

Nisin is used in canned food products in order to prevent spoilage from thermophilic microorganisms. It has been shown that nisin used in the canned vegetables at room temperature increases its shelf-life [136]. Microbes like Clostridium spp., *Clostridium thermosacchrolyticum*, and *Geobacillus stearothermophilus* producing thermophilic spores. Nisin prevents thermophilic spore-forming microorganisms, which are responsible for the food-spoilage and can also be used in canned peas, carrots, potatoes, baby corn etc. [137,138,139]. In addition, nisin is also used as an additive in the storage of fruit and vegetable juices such as tomato juice and mint extract [138]. Nisin is useful for the growth inhibition of acid-tolerant microorganisms, which destroy spoilage of alcoholic beverages beer and wine. It prevents the growth of Lactobacillus, Leuconostoc and Pediococcus which results in the spoilage of beer and wine [140]. nisin is used as an additive in the fermenters in brewing industries. It also enhances the shelf-life of beer [136].

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Some natural antimicrobial peptides are used as a food preservative in the food industry like Pediocin PA-1 is a commercially available bacteriocin, which is being marketed as AltaTM 2341.Pediocin is used in few countries as a food preservative to inhibit the growth of L. monocytogens, which causes spoilage of meat [141]. Enterocin AS-48 is an antimicrobial peptide used for the preservation of cider, fruits, and vegetable juices. Another preservative, Enterocin CCM4231 is used for the preservation of Soya milk [141]. Bovine and activated lactoferrin (ALF) present in milk has the characteristic iron binding ability, which is approved in

the USA as a safe preservative for meat and beef products. Antimicrobial peptides imitative from milk protein like lactoferricin, kappacin and k-casecidin. They possess curious antibacterial activity and useful as food preservatives [142].

Natural antimicrobial peptides are used in the field of agriculture too. Beta-purothionin, cecropin B, and phor21 exhibited antifungal activity in vitro. Their expression under an endogenous promoter with moderate-level activity and extracellular secretion indicated that in plant, only beta- purothionin exhibits high antibacterial and antifungal activity. [143]. Two 38-amino acid peptides, SB-37 and Shiva-1 were produced as substitution analog of Cecropin B, a natural lytic peptide of *Hyalophora cecropia*. First-generation of seedlings expressing Shiva-1 exhibited delayed wilt symptoms and reduced disease severity and mortality after infection with a highly virulent strain of *Pseudomonas solanacearum* compared to control plants [144].

Researchers have shown a genetic modification of potato by AMP-encoding genes. Alfalfa antifungal peptide (alfAFP) isolated from seeds of *Medicago sativa*, displays strong activity against the harmful fungal pathogen of potato, *V. dahliae* [145]. MsrA3, an N-terminally modified analog of temporin A, expressed in potato led to the resistance against two prevalent potato diseases, late blight and pink rot that is caused by *Phytophthora infestans* and *Phytophthora erythroseptica* respectively. The activity of bacterial phytopathogen *E. carotovora* was also inhibited by MsrA3 [146]. MSI-99 in tomato led to the prevention of bacterial speck disease caused by *Pseudomonas syringaep* [147]. Alternaria solani is causes early blight in potatoes it also a highly serious fungal diseases of tomato as it results in crop loss and reduction of fruit quality. only a prevalent but also a highly serious fungal disease of tomato as it results in yield loss and reduction of fruit quality. Tomato lines which had been transformed by the introduction of a gene from *Mirabilis jalapa*, encoding Mj-AMP1, showed enhanced resistance to early blight disease [148]. Rice is a major staple crop and serves as a model cereal crop plant for scientific studies [149]. Rice plants expressing the cecropin A gene of

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Hyalophora cecropia showed enhanced resistance to *Magnaporthe grisea*, the causal agent of rice blast disease. Though both genes expressed properly and products of both of them showed activity against *M. grisea* in vitro, due to negative effect of the latter gene version on fertility, ER-CecA was suggested as a potent candidate for protection of rice plants against the rice blast fungus *M. Grisea* [150]. Devastating rice disease is bacterial leaf blight caused by *Xanthomonas oryzae* pv. Oryzae. Transgenic expression of cecropin B, isolated from *Bombyx mori*, confined lesion development in the infected leaflets [151]. Attacin E is an AMP that originated from *Hyalophora cecropia*. Expression of attacin E in transgenic Royal Gala apple resulted in significant resistance to *Erwinia amylovora*, the bacterial agent that causes fire blight disease [152]. Magainin-type genes in transgenic grapevine led to strong resistance to Agrobacterium vitis, the bacterial agent of crown gall disease, and mild resistance against *Uncinula necator*, the fungal agent of powdery mildew [153].

Conclusions

Natural antimicrobial peptides have broad-spectrum activities against different kinds of pathogens like fungi, viruses, protozoans, Gram-positive and Gram-negative bacteria as well as resistant bacteria. In (2016) wan et al. reported that green tea plant extracted antimicrobial peptides shows great antimicrobial activity against *E. coli*. Different types of microorganisms like yeast, mold, bacteria are mainly responsible for the spoilage of food [154]. Most of them have the ability to grow in stress conditions such as low oxygen and low moisture [155]. Benzoate, propionate, sorbate, nitrate, nitrite, and sulfites are chemical-based preservatives that inhibit the growth of microbes and freezing, chilling, reduction of water-activity, acidification, nutrient restriction, fermentation are traditional methods for food preservation [156]. Due to the use of potential synthetic preservatives an adverse impact on human health and effect indirectly on

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environmental sustainability. Naturally occurring anti-microbial peptides are an alternative way to reduce the chemical burden of synthetic preservatives. NAMPs can be used as natural food preservatives which are less complex, less toxic, eco-friendly, and broad-spectrum. In this review article, we have discussed almost all the different types of NAMPs produced by different sources like plant peptides, animal peptides, fungal peptides, and bacterial peptides. These types of NAMPs are very useful for human welfare, agricultural environmental, clinical, medical microbiology, and could be used as a natural preservative in the food industries. Diverse natural and synthetic peptides with antimicrobial properties have great possibilities for the development of innovative approaches in medical and agricultural biotechnology. They present novel alternatives or substitutes for antibiotics in the treatment or control of microbial infections in humans, animals, and plants and could be used as natural food preservatives. However, more in-depth research is needed to explore unknown natural antimicrobial agents through advanced genomics and metagenomics approaches for better understanding of these NAMPs and uses for the betterment of humans, plants, and animals.

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Abbreviation

اعادة كتابة

Availability of data and material

All data generated or analyzed during this studying are included in this published article

Ethics approval and consent to participate

Not applicable

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Table. 1: Different types of natural bacterial peptides and their potential applications.

Bacterial peptide	**Strain**	**Therapeutic targets**	**Potentials application**	**References**
Nisin	*L. lactis, Streptococcus uberis*	Gram-positive bacteria	Effective against staphylococcal (including MRSA) and enterococcal infections. Medicinal use in bacterial mastitis. Oral hygiene, deodorants.	[23,24,25,26]

Mersacidin	*Bacillus sp*.	MRSA VRE, *C. difficile*	Effective against staphylococcal (including MRSA) and enterococcal infections. Treatment of CDAD (Clostridium difficile associated diarrhoea)	[27,28,29]
Lacticin 3147	*L. lactis*	Gram-positive bacteria	Effective against bacterial mastitis. staphylococcal and enterococcal infections including VRE, Acne.	[30,31,26]
Actagardine	*Actinoplanes sp.*	MRSA, VRE, *C. difficile*	Effective against staphylococcal (including MRSA)and enterococcal infections. Treatment of CDAC (Clostridium difficile associated diarrhoea)	[28]
Gallidermine	*Staphylococus sp.*	Propionibacteria	Skin disorders including acne, eczema, folliculitis and impetigo	[32]
Epidermine	*Staphylococcus sp.*	Stapylococci	Skin disorders including acne, eczema, folliculitis and impetigo	[32]
Duramycin	*Streptomyces cinnamoneus*	Gram-negative and Gram-positive bacteria	Treatment of cystic fibrosis, ocular diseases and disorders	[33]