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

ABSTRACT

The rate of discovery of new antibiotic is slower than the emergence of antibiotic-resistant strains in the environment. This global problem is more acute in developing countries. Therefore, it is necessary to develop some alternative approaches to combat infections caused by pathogenic microorganisms and resistant strains. Natural antimicrobial peptides (NAMPs) are potent antimicrobial peptides 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 in agriculture pharmaceutical and food industries. NAMPs have been used as food preservatives against food-borne pathogens thereby increasing the shelf-life of food items. NAMPs are useful in the treatment of wounds, ulcers, skin and soft tissue infections caused by microorganisms. Different types of NAMPs are universal in nature and show broad-spectrum antimicrobial activities. NAMPs exhibit great potency against multidrug-resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA). They have unique characteristics of targeting multiple pathogenic strains and prevent the emergence of natural resistance. In this review article, we systematically discussed different types of natural antimicrobial peptides, their classification, expression, diversity and source. We also explored their mode of action, genetic regulation and application as an alternative therapeutic agent.

Keywords: *Natural antimicrobial peptides (NAMPs), Animal peptides, Plants peptide, Lantibiotics, alternative therapeutics.*

1. INTRODUCTION

Natural antimicrobial peptides (NAMPs) are promising antimicrobial peptides due to 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 [1]. 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 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 [2]. 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 using 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. 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 in the laboratory conditions and more than 99% of the bacterial strains remain in viable but not culturable (VBNC) state in the environmental samples [3]. These strains cannot be cultured in the laboratory by routine culture

methods and have been ignored by the scientist [4]. 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, make libraries of the DNA fragments and do 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.

1.1. HISTORICAL OUTLOOK OF NAMPs

Alexander Fleming in the late 1920s identified lysozyme and considered it as the first antimicrobial peptide [5], the exact mode of action of lysozyme was not known until 1958 when Salton discovered that lysozyme degrades the bacterial cell wall [6]. Antimicrobial peptides were first noted in prokaryotic cells. The NAMPs were Isolated from *Bacillus brevis* and named as gramicidin, which showed in vitro and in vivo activity against many Gram-positive bacteria [7]. Later, it was declared that Gramicidin is beneficial against infected wounds of guinea-pig and used as a therapeutic agent [8]. In 1941, antimicrobial peptide Tyrocidine was reported with activity against both Gram-positive and Gram-negative bacteria [9]. 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* [10]. Later on, it was named as purothionin [11,12]. In 1956,

antimicrobial peptide defensin was isolated from the leukocyte of rabbit [12]. The antimicrobial peptides lactoferrin was isolated from milk[13,14]. 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* [15]. Prokaryotic peptides such as Hiolbiotics, lantibiotic, and microcin were found to be NAMPs [16].

1.2. 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) [17]. Bacteriocins are lethal to bacteria other than the producing strain and are classified largely based on the differences in their molecular weight. Mode of action of antimicrobial peptides of bacterial origin is by permeabilization of the target cell membranes [18,19]. 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. Lantibiotic is an important natural antimicrobial peptide 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 [20]. 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 [21]. They reveal antimicrobial activity against Gram-positive bacteria by the formation of spore in the cell membrane [22]. Nisin is the first most promising lantibiotic which was discovered in 1920 and used as a food preservative in food industries [23]. The peptide Nisin is

produced by *Lactococcus lactis*. Natamycin is isolated from *Streptomyces natalensis* and used as a food preservative against the food spoiling microorganism, especially yeast or molds. 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 isolated from *Lactobacillus reuteri* and has antimicrobial properties. It is water-soluble non-proteinaceous and effective against Gram-negative and Gram-positive bacteria, filamentous (molds), and nonfilamentous (yeasts) fungi [24]. Reuterin show bacteriostatic activity particularly against *Listeria monocytogenes* and many pathogenic bacteria.

1.3. PLANT NAMPs

Plants secrete antimicrobial peptide as a part of their defense mechanisms against pathogens. They primarily target pathogenic fungi however, antibacterial and insecticidal activities are also reported [36]. Fungicidal mechanisms of most of these peptides remain to be explored [37]. Plant producing antimicrobial peptides are defensins, thionins, lipid transfer proteins, hevein-like peptides. Plant defensins are small, highly stable, cysteine-rich peptides with antifungal properties [38]. They are progressive against *Fusarium spp*., *Saccharomyces cerevisiae*, and *C. Albicans* [39]. Eugenol is a naturally occurring phenolic molecules found in some plants such as cloves. It is extracted from clove buds for use of dental and oral hygiene. It is also used as local anesthesia and the formation of dental materials in clinical dentistry and is very effective against *Salmonella, Shigella*, *Clostridium botulinum*, *Listeria monocytogenes* and *E. coli* [40]. Thionins are one of the major groups of plant NAMPs. α-purothionin is the first thionin which is isolated from wheat endosperm. Expressions of thionins in plant tissues could be initiated by exposure to different pathogens [41]. 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 [42].

1.4. ANIMAL NAMPs

Animal antimicrobial peptides obtained from mammals, amphibians, and fish, etc. Antimicrobial peptides, the mucosal epithelial cells and paneth cells both are produced from mammals. Mammalian leukocytes are a rich source of antimicrobial peptides that protect against bacterial infections. These antimicrobial peptides are cationic in nature [43]. Protamine and Pleurocidin are two major types of animal antimicrobial peptides isolated from fish which have activity against *L. monocytogenes* and other food-spoilage microorganisms. 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). Lactoperoxidase enzyme is very effective against Salmonellae, Shigella, Pseudomonas and coliforms. [44]. Avidin is a positively charged glycoprotein that is present in eggs. Egg also contains biotin. Avidin can effectively inhibit the growth of *E. coli, Klebsiella pneumoniae*, *Serratia marcescens*, and *P. aeruginosa*. [45]. Protamine is a natural food preservative. It is cationic antimicrobial peptide obtained from fish. Protamine shows 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 [46]. Protamine is effective against Gram-positive and Gram-negative bacteria effective against yeast and molds [47].

2. CLASSIFICATION AND DIVERSITY OF NATURAL ANTIMICROBIAL PEPTIDES

Natural antimicrobial peptides are classified on the basis of structures, origins, and mode of action:

2.1. 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 [48,49,50]. Most NAMPs belong to the α-helical and β-sheet. α-helical peptides are typically unstructured in solvent, and becomes amphipathic helical shape when it comes in contact with a biological membrane [51,50]. The two most studied peptides in this group are (i) LL-37 [50, 52] which is produced as an inactive precursor (hCAP18; human cathelicidin) in neutrophils and epithelial cells [53] (ii) human lactoferricin which is derived by proteolytic division of the antimicrobial and immunomodulatory iron-binding glycoprotein lactoferrin present in milk and exocrine secretions [54,55]. β-sheet peptides are maintained by disulfide bonds [56,57] and are assembled to make an amphipathic molecule [51]. The β-sheet peptides are more common in aqueous solution due to rigid structure [51]. The best-studied β-sheet peptides are the defensins that are produced as inactive precursors in neutrophils, macrophages, and epithelial cells [53,50]. 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 [58- 60]. Defensin family peptides range from almost 20-30 amino acids in length and are described by six cysteine residues and intramolecular disulfide bond formation and these peptides can yield to an amphipathic α-helical structure in hydrophobic conditions. [61- 63]. Some natural antimicrobial peptides related 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 [48, 49]. Other NAMPs, many of the extended peptides fold into amphipathic structures after contact with a membrane [49]. The most effective peptides in this group is indolicidin which is derived from bovine leukocytes [56].

2.2. CLASSIFICATION ON THE BASIS OF ORIGIN

Natural antimicrobial peptides are classified on the basis of origin from different sources. Defensin is a very useful molecule which is derived from keratinocyte cells and play an important role in the innate immune system in skin and liver. They have cationic sequences, rich in cysteines [64]. Studies show that these molecules interact with the microorganism through electrostatic interactions with the lipid membrane of the host, generating pores and promoting the death of the microbe by osmotic imbalance

[65]. Human beta-defensin type 2 (hBD-2) is used as a pro-inflammatory molecule in psoriasis and acne lesion stimulated by the existence of *P. acne* bacteria [66]. The bactenecins (Bac5 and 7) were firstly known as mammalian cathelicidin which were synthesized from bovine neutrophils and rabbit CAP18 from granulocytes. In cattles, buffalo, horse, chicken, and fish the multiple cathelicidins are found [67]. Cathelicidins are also secreted from epithelial cells such as keratinocytes, mast cells, neutrophils [68]. The membrane of the *P. acnes* and cathelicidin interact and it is 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 [69,70]. Lactoferrin (LF) is an iron-binding glycoprotein that is part of the innate defense system. The nature of Lactoferrin has antibacterial, antiparasitic, anti-cancer and anti-allergic properties [71]. The LF and Fe^{3+} ion connected to each other and interact with the bacterial membrane directly, and it show antibacterial activity [72,73,74]. The hLF1-11 peptide plays antimicrobial activity against Gram-positive and Gram-negative bacteria and also fungi. The synthetic peptide is also effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Acinetobacter baumannii* strains [75-77]. hLF1-11 is an antimicrobial peptide derived from the N terminus of human lactoferrin. hLF1-11 is used as antibiotic for a synergistic effect and it is effective against fluconazole resistant *candida albicans*. Pre-incubation of fluconazole-resistant *C. albicans* with hLF1-11 naturally increase the candidacidal effect of fluconazole [78]. Thionins are one of the major groups of plant NAMPs. Thionins expression in plant tissues can be induced by various pathogens [41]. The anti-infective mechanism is determined by the interaction between thionins hydrophobic residues and the positively charged membranes of pathogens. The proposed mechanism is associated with the lysis of cell membranes. Another proposed antimicrobial activity is disrupting the calcium influx during the cellular activity which changes the membrane polarity [79]. Berocall-Lobo *et al.* (2009) showed that wheat thionin, antibacterial activity against *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 mainly found in seeds and work as defense molecule against animals. It is highly toxic to plant pathogens. Thionins isolated from barley (*Hordeum vulgare*) involved in the

defense against microbial infections [80]. Some thionins have shown cytotoxic activity and can be used in the development of new drugs against cancer [81]. Thionins is also present in cereals and *Pyrularia pubera* which have four disulfide bonds. The structure of thionins is defined by the G (gamma) fold to be expressed by two antiparallel α-helices that form a stem and antiparallel ß-sheets that form an arm [82].

3. MODE OF ACTION AND THEIR FUNCTION

Natural antimicrobial peptides are found in nature 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 and inhibition of cell wall synthesis [83]. Pore formation causes exposure of low molecular weight compounds (e.g. ions K^+, H^+, phosphate) 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 [84]. 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. The first lantibiotics were Nisin and epidermin that shown to use lipid II as a docking molecule [85]. Nisin binds lipid II through 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 [86]. Nisin inhibits target cells by blocking cell wall formation through the biosynthesis of peptidoglycan layer [87]. A number of different Lantibiotics with N-terminal ring structures similar to nisin kill target cells by lipid II-mediated pore formation [88]. Viscotoxins belong to plant thionins. it is toxic in nature and isolated from both leaves and stems of the European mistletoe (*Viscum album*). Viscotoxins induced the presence of deficiency on the surface of membranes that lead to the destabilization and disruption of the membrane bilayer [89]. Animals producing natural antimicrobial peptide chitosan are obtained from partial deacetylation of chitin. It is a natural polycationic linear polysaccharide largely found in shells of marine crustaceans [90]. It possess antitumor, antifungal, antimicrobial and antioxidant activities [91]. Chitosan is dominant-against Gram-negative bacteria like *Bacteroides fragilis, cholera, Shigella dysenteriae*, *E. coli*,

and *Vibrio*. Mammalian antimicrobial peptide cecropin P1 in transgenic tobacco led to accelerate the resistance to phytopathogenic bacteria *Pseudomonas syringae* pv. tabaci, *Pseudomonas marginata*, and *Erwinia carotovora* [92].

4.GENETIC REGULATION AND EXPRESSION OF NAMPs

NAMPs fall into two categories based on their expression: that is 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 [93]. NAMPs are classified into two groups based on the electrostatic charge. First group have positively charged peptides in large group peptide and second groups consist of non-cationic peptides and its further divided into many subgroups such as aromatic peptide, anionic peptide and peptides [94]. Non-cationic peptides in comparison with the first group are uncommon. Mostly the term antimicrobial peptide only refers to cationic AMPs. Cathelicidin expression occurs at both the transcriptional and post-translational level from the transcripts of human cathelicidin precursor protein (hCAP18), encoded by the gene CAMP, it 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 [95,96]. In mice, the cathelicidin gene for mCRAMP (*Cnlp*) derived from phagocytes is regulated by hypoxia-inducible factor 1α (HIF-1α) [97,98]. The cathelicidin domain acts as both an antimicrobial peptide as well as an inhibitor of protease activity [99]. 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 [100]. AMPs perform role in innate immunity via direct inhibitors of microbial activity through the governance of immune cell function and recruitment and by general mechanism proposed for their mode of action against pathogens. The cationic NAMP is mostly attracted to the negative charge of the membrane on both Gram-positive and Gram-negative bacteria. The peptides harmonize with the bacterial membrane and inserted into the lipid bilayer resulting in the formation of pore or disrupting membrane [101]. This laeds to destabilization of the bacterial membrane and bacterial lysis. The AMP preferentially

targets dividing or nondividing bacteria, especially at the site of cell division [102]. 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 [103]. 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 [104,105]. LL-37, as well as its proprotein, were also found bound to plasma lipoproteins [106-108]. Human beta-defensin-2 increases the level of LL-37 expression in colon and breast epithelial cells [109]. Defensins belong to distinct family of AMP and expressed in mammals, including epithelial cells of the skin, gastrointestinal, reproductive, and respiratory systems [110,111,112]. The Mature defensins are cationic and has positive charge ranging from +1 to +11. The small cationic peptide length is between 28-44 amino acid and contain 6 to 8 cysteine residues which help in the formation of intramolecular disulfide bridges The molecular structure and configuration of these disulfide bridges are the base for the break up these NAMPs into specific subfamilies corresponding to α, β. In humans, α-Defensins made by three disulfide bridges between cysteine residues 1- 6, 2- 4, 3- 5. The α and β-defensins are derived from gene products believed that evolved from an ancestral β-defensin gene [113]. α-defensins suppose to communicate with the antimicrobial host defense within the urogenital tracts, gastrointestinal and circulating immune cells. Human neutrophils encode genes corresponding to the four α-defensins termed as human neutrophil peptides 1- 4 (HNP-1 through 4) [114,115]. The binary function is cover by α-Defensins and the members of the cathelicidin family, as both are modulator of microbial pathogenesis via 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 [116].

5. APPLICATION 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 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 [117]. Nisin show antimicrobial properties against food spoiling bacteria like *Listeria monocytogenes* [118]. It used in veterinary medicine and the treatment of bovine mastitis [119]. Nisin is effective against clinically relevant human pathogens like *Helicobacter pylori*. Actagardine and mersacidin appear to have notable activity against methicillin resistant, *Staphylococcus aureus* infection, oral decay and acne [120]. Both Gallidermin and Epidermin are used in the treatment of human diseases like acne, eczema, folliculitis, and impetigo and also used for personal care products. Cinnamycin is used in inflammation, viral infections and for blood pressure regulation[121]. Pep5 and Epidermin prohibit the attachment of coagulase-negative Staphylococci specifically *S. epidermidis* to silicon catheters [122]. Mutacin 1140 can prevent dental cavities. Duramycin and Ancovenin both are used for the treatment of inflammation and blood pressure regulation. Natural antimicrobial peptides from animals and plant origin are used as alternative to chemical preservatives because of the safety, no toxic effects, and elongation of shelf life of food products [123]. Bacteriophages are also used as a preservative for food items. *Lactobacillus reuteri* is a water-soluble, non-proteinaceous in nature. It is effective against many microorganism like Gram-negative, Gram-positive bacteria, filamentous (mold), and non-filamentous (yeast) fungi [124]. NAMPs have diverse applications and can be used as therapeutic agents against bacterial, fungal, and viral infections. NAMPs are effective against some antibiotic-resistant bacteria like methicillin-resistant *S. aureus*, Vancomycin-resistant *enterococcus* (VRE). Some NAMPs are also used in agricultural like b-purothionin, cecropin B, and phor21 which show antifungal activity. Alfalfa antifungal peptide isolated from seeds of *Medicago sativa*, and it show activity against the unstable fungal pathogen of potato, *V. dahlia*. Rice plants expressed the *cecropin A* gene of *Hyalophora cecropia* which provide resistance to *Magnaporthe grisea*, a specific agent of rice blast disease. It will be crucial for the development of NAMPs for practical use in medicine as a therapeutic agent. Natural antimicrobial peptides play an important role in humans, animal diseases, agriculture and the environment. The preservation of the chicken and meat is done by Defensin. Various bacteriocins are known to target pathogens, including *Clostridium difficile* and emerging antibiotic-resistant bacteria such as methicillin resistance *staphylococcus aureus* (MRSA), vancomycin resistance *enterococcus* VRE and entero-hemorrhagic *E. coli* [125-127]. Recently,

313 researchers have shown that bacteriocin based therapeutic approaches might be a part of the treatments
314 against pathogens. For example, bacteriocin therapy used in distal colon models and demonstrated that
315 the narrow-spectrum bacteriocin (sactibiotic) thuricin CD specifically eliminates *C. difficile* without
316 disrupting the beneficial microbial community [128]. Use of bacteriocin might prove good to present
317 treatment for *C. difficile* associated intestinal diseases using a broad spectrum of antibiotics [129].
318 Lantibiotics (such as nisin, mersacidin and lacticin 3147) can eradicate infections caused by *Strep.*
319 *pneumonia* and MRSA in mice [130,131] as well as having preventive effects against tooth diseases in
320 dogs [132] and bovine mastitis in dairy cows [133]. Bacteriocin (microcin J25) isolated from gram-negative
321 bacteria have been shown to drastically reduce *Salmonella* infection in a mouse model [134]. Nisin was
322 one of the first NAMPs which show great potency in animal infection model. Nisin can be eliminated from
323 the blood very rapidly like penicillin [135]. Lysostaphin is a (bacteriocin) produced by *S. simulans* [136],
324 the group of antimicrobial proteins that enzymatically degrade bacterial cell wall [137]. Nisin is also used
325 in canned food products to protect spoilage from thermophilic microorganisms like *Clostridium spp*.,
326 *Clostridium thermosacchrolyticum*, and *Geobacillus stearothermophilus* produce thermophilic spores
327 [138]. Nisin protect thermophilic spore-forming microorganisms, which are responsible for the food-
328 spoilage and used in canned peas, carrots, potatoes, baby corn etc. [139,140,141]. It inhibits the growth
329 of *Lactobacillus* and *Leuconostoc* which results in the spoilage of beer and wine [142]. Nisin is used as an
330 additive in the fermenters in brewing industries. It also enhances the shelf-life of beer [138]. Pediocin PA-
331 1 is natural antimicrobial peptide which is used as a food preservative in the food industry. Some
332 countries are using Pediocin PA-1 as a food preservative to stop the growth of *L. monocytogenes*, which
333 causes spoilage of meat [143]. Enterocin CCM4231 is used for the preservation of Soya milk [143].
334 Bovine and activated lactoferrin (ALF) present in milk has the characteristic iron binding ability, US-FDA
335 approved the lactoferrin as a safe preservative for meat and beef products. Lactoferricin, kappacin and k-
336 casecidin show antibacterial activity and also useful as food preservatives [144]. Natural antimicrobial
337 peptides are Beta-purothionin, cecropin B, and phor21 used in the agriculture for exhibited antifungal
338 activity in vitro. Their expression under an endogenous promoter with moderate-level activity and
339 extracellular secretion indicated that in plants, only beta- purothionin exhibits high antibacterial and
340 antifungal activity [145]. SB-37 and Shiva-1 are 38-amino acid peptides similar to Cecropin B which is a

natural lytic peptide of *Hyalophora cecropia*. Shiva-1 is very effective against virulent strain of *Pseudomonas solanacearum* compared to control plants [146]. 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* [147]. 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 [148]. MSI-99 in tomato led to the prevention of bacterial speck disease caused by *Pseudomonas syringae p* [149]. *Alternaria solani* is caused by early blight in potatoes; it is also a highly serious fungal disease of tomato as it results in crop 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 [150]. Rice is a major staple crop and serves as a model cereal crop plant for scientific studies [151]. Rice plants expressing the *cecropin A* gene of *Hyalophora cecropia* showed enhanced resistance to *Magnaporthe grisea*, the causal agent of rice blast disease. ER-CecA was suggested as a potent candidate for protection of rice plants against the rice blast fungus *M. Grisea* [152]. 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 [153]. 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 [154]. 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 [155].

6. 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 show antimicrobial activity against microorganisms like yeast, mold, bacteria[156]. Most of them have the ability to grow in stress conditions like low oxygen and low moisture [157]. Chemical-based preservatives are Benzoate, propionate, nitrate, nitrite, and sulfites stop the growth of microbes. Freezing, chilling, reduction of water-activity, acidification, nutrient restriction, fermentation are physical methods of food preservation [158]. Natural antimicrobial peptides are an alternative option 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, environment, 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 and applications of these NAMPs for the betterment of humans, plants, and animals health.

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CONFLICT OF INTEREST

On behalf of all the authors, the corresponding author sates that there is no conflict of interest for this article.

COMPETING INTEREST

There is no competing interest for this article.

AVAILABILITY OF DATA AND MATERIALS

N.A.

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