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Review Article

Microbiome-induced Antimicrobial Peptides: The Host-defense Weapon Unravelling Drug Designing

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Abstract

The present review discusses about the contribution of microbiome that secrete antimicrobial peptides in association with residing microflora of the host imparting antimicrobial activity against invading pathogens. The relationship between antimicrobial peptides and microbiota of the intestine and their resultant effects on host health are highlighted. Defensins, cathelicidins, brevinins, ranalexin etc. can be harnessed as potential therapeutic targets for diseases like ileal Crohns disease, inflammatory bowel disease, colon cancer, etc. The bottom line is to make use of the antimicrobial peptides over the years to scientifically respond to infective agents in terms of therapeutic options in the treatment of animal diseases.

Keywords: AMPs, Defensin, Microbiome, Paneth Cell

Introduction

The intestine is a complex ecosystem consisting of microflora, nutrients and host cells for digestion, absorption and assimilation of available nutrients together. The gastrointestinal tract, serving as point of entry for microbes, have innate immunity of complex defence mechanisms for protection against pathogens. The intestinal disorders occur due to disparity among the existing offending and defending factors. Many antimicrobial peptides (AMPs) help in curing these intestinal disorders through innate mucosal immunity. Increased expression of numerous microbiome-induced AMPs is due to increased microbes' colonization in the intestine lumen. Gut microbes can break down food to provide energy or may invite allergy, therefore the subject of mucosal immunology is one of the strange biology. The microorganisms of gut hold strong influence on physiological processes like food metabolism, cell growth, cell differentiation, mood and behaviour change (Johnson, 2020). Scientific groups are now in favour to consider gut microbiome as second genome of human body (Ho and Ross, 2017). Initially the mother's womb is a microbe free environment. Now, question arises how a growing human embryo developing inside a microbe free environment in mother's womb, gets colonized with bacteria? What is the contribution of the mother? Consensus among scientific community has established vertical transmission of the microbiome from mothers to their children. Metagenomic analysis has established microbiota conservation within humans and other hominids suggesting an ancient assembly selected host fitness optimization (Blaser, 2006). Maternal body surface microorganisms and environment are the initial sources of colonization process of the gut starting at birth (Mulder *et al.*, 2009; Dominguez-Bello *et al.*, 2011). Initial microbial community during neonatal period is variable and unstable for a considerable period of time and subsequently it attains stability to become adult type within three years of age (Koenig *et al.*, 2011). Metagenomic analysis has confirmed the presence of 10-fold more microbial cells in gut than eukaryotic cells in the human body, that amounting to 100 times more genes than the entire human genome (Gill *et al.*, 2006). Researchers confirmed the presence of about 10^{14} bacterial commensals of 1000 different species colonizing mammalian gut (Turnbaugh *et al.*, 2007) giving shape to host immune system (Ivanov and Honda, 2012).

AMPs produced by the intestinal epithelium and the gut microbiota mainly in the pylorus, fundus, pyloric caeca and anterior intestine areas (Çinar *et al.,* 2001). These small cationic amphiphilic peptides having multifunctional activities and work as effectors of innate immunity with direct antimicrobial effect against various fungi, viruses, bacteria and parasites (Gordon *et al.,* 2005). The complex defence mechanism protects host through defensive factors of local immune system, i.e., the gut associated lymphoid tissue (GALT), the microflora itself and the mucosal barrier. The human defense peptides confer broad spectrum of action while the bacterial defense peptides have much narrower spectrum as they specifically bind to cell envelope receptors with high affinity (Martínez *et al.,* 2016). Commercially available AMPs can serve as potential therapeutic antibiotics for treating veterinary and human microbial diseases (Rabanal and Cajal, 2016, Sharif *et al*., 2017). The worldwide emergence of antibiotic-resistant bacteria has raised the spectra of a post-antibiotic era where common infections and minor injuries can become life threatening (Mukherjee and Hooper, 2015). Hence, the discovery of novel therapeutic interventions from intestinal AMPs with the potential to rejuvenate host cell defence will be a step forward in upholding the immunity level of the animals.

Colonisation of Microbiota in the Intestinal Tract of New-Borns

Infants are born with a sterile gut which is colonized initially by maternal flora followed by environmental flora. First microbes get entry into infant through birth canal, skin of mother. Life time association then comes from breast milk, air at neonatal place, home life, pets and then school (Peccia and Kwan, 2016). The infantile floras evolve toward a normal adult flora, but the time course depends on the infant's diet. During the first 24 hours of new-born life, the first colonizing bacteria are *Escherichia coli and Enterococcus* spp. In case the baby is breastfed, obligate anaerobes like *Bifidobacterium* spp., *Bacteroides* spp., etc. appear rapidly but in formula milk-fed babies, *Escherichia coli*, *Clostridium difficile*, *Prevotella* and *Lactobacillus* predominate as oligosaccharides in infant formula are different from those naturally human milk, and thus having no beneficial effects on breast-fed neonates (Walker, 2000; Bourlioux *et al.,* 2002).

Major physiological function of the resident microbiota prevents pathogen infection and acts as a microbial barrier. Intestinal microbiota influences the immune response through cytokine network, such as IL-12 production, determination of Th1 and Th2 responses, and production of antibacterial substances by resident gut microbiota, such as AMPs (Lievin-Le Moal *et al.,* 2006). Metagenomics analysis revealed that 90 % of the bacterial phylotypes are members of two phyla Bacteroidetes and Firmicutes, followed by Actinobacteria and Proteobacteria (Qin *et al.,*

2010).

Evolution of AMPs and its Relation with the Body's Defense Mechanism

Nearly 30 years ago at the Department of Microbiology, University of Umeia in Northern Sweden, Hans Boman was curious to know how do animals survive when infected with fast multiplying pathogenic microbes and having with slow acting adaptive immune system. The animals lacking adaptive immune system, like insects neither secrete antibody, circulating T-lymphocytes nor natural killer cell, but still protect themselves from microbial environment. Survival seems to be virtually unattainable in absence of inherent shield of innate immunity. But interestingly, plants, fungi and invertebrates where adaptive immunity is completely lacking, successful survival is made possible by their innate defense mechanism alone. It was postulated that some chemical substance (other than antibody, cytokine or complement) secreted from those multicellular organisms might be playing some role which acts instantly on pathogens to reduce the microbial load as a safeguard mechanism. That was the real beginning of AMP search (Boman, 1972). From these initial studies with Drosophila, an array of insect AMPs and other immune peptides were characterized. The earliest AMP was identified and isolated from the pupae of silk worm (*Hyalophora ceropia*), which when induced with bacteria, secreted a peptide, scientifically named as *ceropin*. Ceropins have so far been isolated in higher insects as well as from pig intestine. Lysis of *E. coli* was the common assay procedure adapted to prove the antimicrobial property of ceropin (Hultmark *et al.,* 2005). The intention of this article is not to write a review on AMPs rather to describe the importance of AMPs in host innate immunity in gut due to presence of microbiota. New external environment strains of pathogenic and non-pathogenic bacteria colonization are resisted by the existing colonic microflora. Several mechanisms act singly or combinedly like competition for the same substrate or mucin adhesion receptor site, production of a physiologically restrictive environment with respect to pH, redox potential, in vivo antibiotic substances (bacteriocin) production and production of a signal molecule acting on survival genes (Fons *et al.,* 2000; Mi *et al.,* 2017). Epithelial cells provide the first line of contact for gut bacteria as they line the lamina propria of the small and large intestines and the Peyer's patches. Tight junctions made up of claudins, occludins, and F-actin (Turner, 2009) and transmembrane protein bridge the adjacent cells of epithelium. In summary, the intestinal microbiome provides a barrier made up of specialized cells producing mucus, AMPs together with resident commensal microbiota, acting as the front line of defence against pathogenic microorganisms. Thus, AMPs are rewarded as templates and may be potential candidates for successful antimicrobial therapy in future.

AMPs: Classification, Structure and Chemistry

AMPs have been described as evolutionary ancient weapons of host against pathogen. We can describe AMPs simply as gene encoded, ribosomally synthesized polypeptide, having less than 100 amino acids residues (da Costa, 2015; Mi *et al.,* 2017). Natural-derived AMPs can be formed by ribosomal synthesis and non-ribosomal peptide synthesis. AMPs derived from microbes exhibit extreme diversity as they are non-ribosomally synthesized by microbes and modified post-translationally/co-translationally. The majority of fungal and bacterial derived peptides are non-ribosomally synthesized peptides having atypical amino acids (Mi *et al.,* 2017). Non-ribosomally synthesized peptides are assembled by enzyme peptide synthetases as opposed to ribosomal-supported synthesis. Polymyxin B, vancomycin, bacitracin and gramicidin are examples of non-ribosomally synthesized AMPs which are effective research tools, but unsuitable for novel applications due to emerging bacterial resistance, like vancomycin-resistant *Staphylococcus aureus* and *enterococci*.

Our subsequent discussion has received emphasis on ribosomally synthesized AMPs and non-ribosomally peptides have been excluded intentionally. AMPs are ribosomally synthesized peptide molecules produced by nearly all organisms, from bacteria to plants and animals regulating the composition and number of intestinal microbiotas (Hof *et al.,* 2001). For the first time in the 1950s and 1960s, the presence of cationic proteins in human neutrophil having bactericidal activity was detected and named as defensin (Rahnamaeian, 2011). Alternatively, AMPs are low molecular peptide of 10–60 amino acids having nearly 50 % hydrophobic cationic residues as Arg, Lys, His (Berg,1996), Cys and Pro residues (Nguyen *et al.,* 2011). The most prevailing structure of AMPs are β-sheet and α-helical molecules (Wu and Hancock, 1999). The major four groups of AMPs as per secondary structure (Sato and Feix, 2006) are linear α-helical peptides alamethicin, cecropin, PGLa, magainin, melittin, mastoparan; cyclic peptides with β sheet structure like tachyplesins, defensins, protegrins, and gallerimycin polymyxin B, tyrocidines, arenicins; peptides with β-hairpin or looped configuration are lantibiotics produced by Gram-positive bacteria, and linear peptides particular amino acid such as proline, tryptophan, histidine or arginine. AMPs predominantly

synthesized by insects such as drosocin, metchnikowin, apidaecin, abaecin, formaecin, lebocin, pyrrhocoricin, metalnikowin, indolicidin, histatin, tritrpticin, tryptophan, diptericins, attacins are included in this group (Berg,1996).

The cationic force defines their selectivity by negatively charged cytoplasmic membranes, while their hydrophobicity by its interactions with fatty acids of bacterial cell lipoprotein layer (Janeway *et al.*, 1999; Allaire, 2018). AMPs demonstrate host defence by disrupting and depolarizing inner bacterial membranes causing rapid cell death (Schroeder *et al.*, 2015). AMPs expression and microbial colonization rises along the intestine although the bacterial population is very low from the duodenum to the proximal ileum (Kopp *et al.*, 2015). Intestinal epithelial cells, chiefly enterocytes, enteric neurons, tuft cells, enteroendocrine cells and secretory cells like goblet cells producing mucin and paneth cells secreting AMPs create a physical and biochemical barrier between the host and microorganisms preventing infections (Aresti Sanz and El Aidy, 2019). AMPs are generated by both epithelial secretory cells and classic immune cells (macrophage, lymphocyte, dendritic cells) present in the lamina propria (Mor and Nicolas, 1994). AMPs are also produced effectively by several other types of cells in the body apart from the intestinal epithelium and gut microbiota (Table 1).

Table 1: Mechanism and therapeutic utility of microbiome-induced AMPs

AMPs	Place of secretion/Source	Mechanism of AMPs	Therapeutic utility	Reference
Defensin **α**	Paneth cells, monocytes, macrophages, T and B cells, dendritic cells	Pore-formation	Ileal Crohn's disease, graft-versus-host disease	Jager *et al.*, 2010; Sivieri *et al.*, 2017
Defensin **β**	Epithelial cells of small and large intestine, monocytes, monocyte-derived dendritic cells	Pore-formation and chemotactic	Colonic IBD.	Hassan *et al.*, 2012
			Bactericidal against *S. aureus, P. aeruginosa, E. coli, L. monocytogenes, S. typhimurium, C. difficile, C. albicans, B. fragilis, E. faecalis, S. pyogenes*.	
Brevinins	Skin of *Rana brevipoda*	Membranolytic	Bactericidal against *E. coli, Bacillus megatherium, S. aureus.*	Duquesne *et al.*, 2007
Esculentin 1a,1b	Skin of *Rana esculenta*	Membranolytic	Bactericidal against *C. albicans, S. cerevisiae* and *Pseudomonas aeruginosa.*	Duquesne *et al.*, 2007
Ranalexin (pipinin/ brevinin-l/ ranalexin)	Skin of the bull frog *Rana catesbaeiana*	Membranolytic	Bactericidal *against E. coli. Bacillus megatherium, S. aureus.*	Duquesne *et al.*, 2007
Cathelicidin	Epithelial cells, leukocytes, Enterocytes, macrophages	Pore-formation	Colonic CD, colon tumour, colon cancer.	Duquesne *et al.*, 2007 ; Sassone-Corsi *et al.*, 2016
LL-37			Bactericidal against *E. coli, K. pneumonia, P. aeruginosa, N. gonorrhoeae, Streptococcus sp., H. pylori, Shigella sp., Salmonella sp., C. albicans.*	
Lysozyme C	Gastric, pyloric and duodenal glands, small intestine, macrophages, monocytes	Peptidoglycan hydrolysis	Antimicrobial against Gram-positive bacteria.	Tang *et al.*, 1999

Currently, microbiome-induced AMPs are being highlighted as they serve as perfect mediators for information exchange among gut bacteria, organs, tissues as modulators of immune and neuronal operations (Hassan *et al.*, 2012). The Gram-positive bacteriocins producers belong to lactic acid bacteria group that ferment sugar into lactic acid. The Gram-negative bacteriocins are referred to as microcins (small peptides) or colicins (large proteins) (Hassan *et al.*, 2012). These microcins are classified as class I (<5 kDa with post-translational modifications) and

class II (5–10 kDa without post-translational modifications) (Nguyen *et al.*, 2003). The formation of essential bacterial molecules is mimicked by microcins like MccJ25 and MccE492 which act as natural receptors of these ligands and enter into the target bacteria. After entering into the susceptible bacteria, the harmless microcins like MccC7 and MccC59are are converted into toxic forms and kill them (Zanetti *et al.*, 1995). Therapeutically, microcins production is also engineered by the enteric bacteria that are effectively displaced from their niche (Sassone-Corsi *et al.*, 2016). The microbicidal activity for AMPs includes mechanisms like formation of pores, depolarisation of membrane, disruption of energy metabolism of bacteria and interference of biosynthetic pathways.

Five different AMPs and proteins namely, defensins, cathelicidins, lysozyme C, phospholipase A2 and REGIIIα/β/γ are produced by paneth cells (Porter *et al.*, 2002). These peptides work in a synergistic manner and have specialized activities against several microorganisms. Paneth cells localized at the bottom of intestinal crypts secrete α-defensins in response to bacterial antigens like muramyl dipeptide, lipopolysaccharide, etc. The induction of AMPs by probiotic bacteria recently demonstrated in bees and other species suggests broad mechanisms revealing potentially important future therapeutic target.

1. Defensins and Antimicrobial Activities

The mucosal barrier extends defence mechanism by production of small defensins acting as endogenous antibiotics with activity against bacteria (Gram positive and Gram negative), viruses, protozoa and fungi (Hancock, 2001). The α defensin is the classical defensin derived from neutrophil while β defensin is slightly larger molecule (Zhao *et al.*, 1996). Plasma concentration of α defensin in human is about 40 ng/ml, which shoots to 2-3 times during inflammatory condition and micromolar concentration during sepsis to arrest pathogenesis. The θ (theta) defensin expressed in granulocytes of rhesus monkey and other primates is derived from 76-amino-acid α-defensin-related precursors (Nguyen *et al.*, 2003). Presently, human and monkeys are no more producing θ (theta) defensin due to evolution and mutation (Harwig *et al.*, 1996). These peptides are secreted into the lumen through paneth cells (Cobo and Chadee, 2013; Aresti Sanz and El Aidy, 2019) and β-defensins are principally generated by epithelial cells (Russell, *et al.*, 1996). Defensins act through chemokine receptor CCR6 and have chemoattractant effect on immature dendritic cells and CD4+ T cells (Dutta, and Das, 2015). They form micropores in the bacterial cell membranes leaking the content of cell with loss of cell structure and cell death ultimately (Russell *et al.*, 1996). Immune cells like monocytes, macrophages, T cells and B cells produce human defensins (Ouellette *et al.*, 1994). Injury or exposure to lipopolysaccharide leads to increase in synthesis of bovine lingual and tracheal **β** defensins (Hristova *et al.*, 1997; Gurao *et al*., 2018). The α-defensins of paneth cells in human and mouse are very potent with selective activities against different types of microbial cell targets. HD-5 plays crucial role as an antibacterial agent by acting against *Listeria monocytogenes*, *Escherichia coli*, *Salmonella typhimurium*, as well as an antifungal agent against yeast-like fungus *Candida albicans*. Cryptdins show cidal effect against ML35 strains of *Escherichia coli*, *Staphylococcus aureus* and *Salmonella typhimurium (*Lencer *et al.*, 1997). Cryptdins 2 and 3 shows very good sensitivity against the trophozoites of the enteric pathogen, *Giardia lamblia* in compared to cryptidins-1 and 6 (Zanetti, 2005). Paneth cell α-defensins are microbicidal inducing chloride secretion in the apical surfaces of T84 cells (Zanetti *et al.*, 1995). Defensins are attractive targets for diseases where the GI functions are hampered.

2. Cathelicidins and Antimicrobial Activities

Cathelicidins, the second largest family of AMPs in mammals, were first reported in cattle myeloid bone marrow cells. They include the bactenecins, Bac5 and Bac7p bactericidal against *Escherichia coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae* and bacteriostatic against *Enterobacter cloacae*. Cathelicidins have polypeptides with conserved N-terminal precursor known as cathelin domain (Harwig *et al.*, 1996). AMPs produced in animals and plants are protegrins, tachyplesins with antifungal, antibacterial activities and retain efficacy in high-salt environments like blood and tissue fluids **(**Zanetti, 2004). In rodents and human single gene codes for cathelicidins, whereas several genes are involved for pigs, cattle and horses (Zaiou and Gallo, 2002). In humans, the cathelicidin is synthesized as an inactive precursor protein known as human cationic AMP of 18 kDa (hCAP18) (Xhindoli *et al.*, 2016).

The LL-37 cathelicidin, synthesized as a propeptide only in human, form mature peptide showing desired antimicrobial activity (Mason and Taylor, 1975). It works by disrupting bacterial membrane by formation of several pores (Diamond *et al.*, 2009). Lysozyme C, a glycoside hydroxylase that cleaves specific residues of peptidoglycan causing bacterial membrane lysis was initially expressed in Paneth cells (Han *et al.*, 1983).

Mechanism of Cellular Defense of AMPs

The molecular basis of functions of peptides is based on attraction owing to its own charge and amphipathic character. The attraction is result of electrostatic interaction of cationic peptides and anionic moieties on the bacterial membrane including lipopolysaccharide and negatively charged lipids in Gram-negative outer membranes and teichoic acids in Gram-positive bacteria membranes. AMPs in phospholipid membrane cross the polysaccharides in external capsule to reach lipid layer present internally for attachment. The Arg and Trp residues stabilizes the interaction of peptide-membrane and of lipid bilayers interfacial regions for membrane insertion.

Once AMPs bind to the surface membrane, an energetically favourable secondary structure as per the hydrophobicity of the peptide is adopted. In case of low peptide/lipid ratios, defensins get embedded parallel to the lipid head groups resulting in membrane stretching. With increasing peptide/lipid ratios, pores are formed and membrane thinning occurs. In high peptide/lipid ratios, pores are formed in critically thin membrane when peptides become perpendicular and are inserted into the bilayer. Different AMPs and different microorganisms have diverged models of membrane permeation. The carpet model shows peptide aggregation on the bilayer surface. With concentration increase, the peptides get into the membrane in a detergent like fashion where the water core gets lined by lipid head groups and inserted peptides. The membrane disintegrates and forms micelles when it reaches threshold concentration. The barrel-stave concept q2 is observed in magainin-2 activity. The peptides form a bundle in the membrane with a central pore like a barrel, with the AMPs as the staves. The toroidal pore model shows activity of magainin, protegrin, and melittin and involves aggregation on the membrane surface. The continuous bend formation occurs through interaction of polar head groups of the lipids and polar faces of the peptides. The toroidal pores are created in membrane causing micelles formation from lipids and membrane disruption subsequently. AMPs with lesser hydrophobicity aggregate parallel to the membrane surface augmenting proper interaction with polar surface areas as insertion into bacterial cells is not always required in peptide mediated killing (Cuthbert *et al.,* 2002). To summarize the above mechanisms irrespective of chemical and structural dissimilarity, most of the AMPs acts against target (cholesterol free negatively charged membrane) through a mechanism involving membrane disruption and pore formation, allowing efflux of essential ions and nutrients. The molecular mechanism of membrane permeation may vary depending upon other parameters like amino acid sequence, peptide concentration and membrane lipid composition. Importantly these peptides are able to kill transformed or cancerous cells. Cytotoxicity is neither species specific nor selective. AMPs promote angiogenesis, chemotaxis, cytokine secretion, histamine release, lipopolysaccharide binding ability that potentiate adaptive immune response.

Therapeutic Potentials with Pros and Cons

From the moment an antibiotic is introduced in the clinics, its useful lifetime begins to tick down. Honestly, we have to accept that new drug development is not an easy task, all the low hanging fruits have already been picked up. It has been observed that epithelial cells of gnotobiotic piglets reared in pathogen free environment too secret antibacterial peptide, where pathogen can enhance the secretion. It indicates that all these AMPs are constitutive rather than adaptive. Therefore, either to replace antibiotic or to reduce the use of antibiotics, other alternative like AMPs may bring some relief to overcome such situation, as bacteria are not yet mutated to that extent to be resistant against AMPs.

Paneth cells secreting HD5 and HD6 are usually localized to the small intestine. Reduced expression of defensins or their absence leads to intestinal Crohn's disease. Thus, different defensin profiles may be the cause of regional localization of ileal or colonic Crohn’s disease (Fellermann *et al.,* 2003, Pruthviraj *et al*., 2018). The immunomodulators like corticosteroids, azathioprine or aminosalicylates (currently available treatments) for inflammatory bowel disease have no significant changes on antimicrobial defensins expression (Kübler *et al.,* 2009). Several antibiotics and probiotics are successfully proved useful in the management and treatment of GI disorders (for example probiotics namely *Escherichia coli* Nissle 1917 strain in ulcerative colitis) (Kruis *et al.,* 2001, Rewatkar *et al.,* 2019)**.** Up-regulation of HBD-2 expression in intestinal epithelial cells is seen in case of *Escherichia coli* Nissle 1917 strain, Lactobacilli and pedicoccus, etc. The simultaneous use of antimicrobials decreases the chances of resistance, increases efficacy, and provides a wide spectrum activity (Poirel *et al.,* 2018; Mo *et al.,* 2019; Mulani *et al.,* 2019). The golden era of natural antibiotic discovery together with optimization of medicinal chemistry of prevailing molecular scaffolds puts pressure for development of new antibiotic molecular frameworks (Walsh and Wencewicz, 2014). AMPs that were trivial few decades ago have now revolutionized the subject of natural evolution and still have potential to inhibit or kill microbes. Moreover, the microbes are still not prepared to

avoid the fatal blow of AMPs. Thus, the AMPs can be an important breakthrough forming basis of a newer class of antibiotics to be employed in the treatment of small and large animal diseases (Pasupuleti *et al.*,2012). Since the AMPs are native to all living beings offering host defense, these peptides have potential to become an entirely new therapeutic approach against several microbial infections. However, these AMPs have to clear their therapeutic promise, their underlying mechanism needs to be investigated and their unwanted toxicity should be tested so that they can be manufactured consistently and cost-effectively in a large scale (Hancock and Sahl, 2006).

Critics have raised some doubts whether microbes may undergo mutation to be refractive towards these peptides in due course of time or not? There may be some valid reason yet the available research reports have indicated that: as low as one in 10^7 or even one in 10^{10} bacteria may be resistant to conventional antibiotics, whereas resistance to AMPs has not been reported to arise naturally. As absolute resistance or susceptibility to any antibiotic is never expected; it has also been recorded that repeated subculture on sub inhibitory concentrations of cationic AMPs can induce resistance, which is linked to production of proteases or alteration of membrane composition. AMPs have a vast range of targets. Strictly speaking, these peptides have the capability of targeting any organism with cholesterol free, negatively charged membrane. The targets are enveloped viruses like HIV, herpes viruses, vesicular stomatitis virus etc.; Gram negative and/or Gram-positive bacteria; fungi; parasites such as trypanosomes, plasmodium etc. and transformed/cancerous cell.

AMPs as novel antibiotics harbour great therapeutic potentials and the beneficial effects outscore the adverse effects. They can be used as novel antibiotics since they convey molecular simplicity, low resistance, broad range anti-microbial activity and immunomodulatory property. At the beginning the production of AMPs may involve high production cost but in latter stage can serve as for the host's native peptides in the treatment of diseases of man and animals (Goswami and Kumar, 2011). One of the recent reports demonstrates that oral administration of probiotics *Lactobacillus casei* CRL 431 and *L. paracasei* CNCM I-1518 in adult mice increases the number of paneth cells and intestinal antimicrobial activity against *Staphylococcus aureus* and *Salmonella typhimurium* (Cazorla *et al*., 2018).

Conclusion

AMPs are integral and crucial component and demonstrate potent antimicrobial activity by neutralizing a broad range of microbes, including viruses, bacteria, protozoa, and fungi. The microbiome-induced AMPs prevent and cure several diseases like ulcerative colitis and Crohn's disease. New insights in the genetics of AMPs and their respective pathways of induction, regulation, and secretion by strengthening barrier defence on epithelial surfaces are studied which can serve as therapeutic ports for future drug designing and development. AMPs, encoded by the mammals, are inducible and crucial components of host defenses against infection. These peptides are attractive candidates with potential template for the development of antimicrobial and immunomodulatory therapies. Notwithstanding lot of antimicrobial development, the emerging resistance of antibiotic has put a spotlight on the urgent need to develop new antibiotic compounds that are highly active, selective and safe. Human defensins, cathelicidin and other AMPs from plants, bacteria, viruses, vertebrates, and invertebrates have a multidimensional signature universally. Although there is availability of quite good range of potential synthetic peptides having antimicrobial activity, but only a small segment has been studied systematically and tested. Moreover, this field remains to be in a stage of infancy and needs to be matured. As of now, the use of AMPs as single therapeutic antibiotic agents has received the significant attention. It is worthy to note that these are the formative years of investigation to elucidate the intricate roles of these versatile peptides in naturally occurring diseases affecting human and animal species. Thus, it would be appropriate to conclude that AMPs have apparent clinical significance as therapeutic agents for treating of human and animal diseases.

Conflict of Interests

There is no conflict of interest.

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