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Gut microbiota and antimicrobial peptides

Katia Sivieri[1], Juliana Bassan[1], Guilherme Peixoto[2] and Rubens Monti[1]

This mini-review covers the potential interactions between gut microbiota and antimicrobial peptides, as well as the main mechanisms of action of antimicrobial peptides. One of the most efficient molecules produced by resident gut microbiota are peptides, which have antimicrobial functions and an innate immune response against infectious agents. Currently, more than 2300 AMPs have been isolated. The human gut microbiota regulates the production of defensins, cathelicidins, C-type lectins, ribonucleases, and S100 proteins in intestinal epithelial cells and Paneth cells, which rapidly kill or inactivate invading microorganisms. The study of gut microbiota and new peptides provides perspective for the synthesis of analogous molecules as an alternative in solving the problem of multidrug resistance reported with conventional antibiotics.

Addresses
[1] UNESP—Univ Estadual Paulista, Faculty of Pharmaceutical Sciences, Department of Food and Nutrition, Rodovia Araraquara Jaú/Km 1 s/n, 14800-903 Araraquara, SP, Brazil
[2] UNESP—Univ Estadual Paulista, Faculty of Pharmaceutical Sciences, Department of Bioprocesses and Biotechnology, Rodovia Araraquara Jaú/Km 1 s/n, 14800-903 Araraquara, SP, Brazil

Corresponding author: Sivieri, Katia (sivierik@fcfar.unesp.br)

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Introduction

The relationship between the host and gut microbiota is very complex and can result in the production of various metabolites [1]. The intestinal epithelium provides a barrier made up of specialized cells producing mucus, antimicrobial peptides (AMPs), and antimicrobial molecules, which, together with resident commensal microbiota, act as the front line of defense against pathogenic microorganisms [2]. In this review, we therefore aim to examine the importance of gut microbiota and its relationship with AMPs.

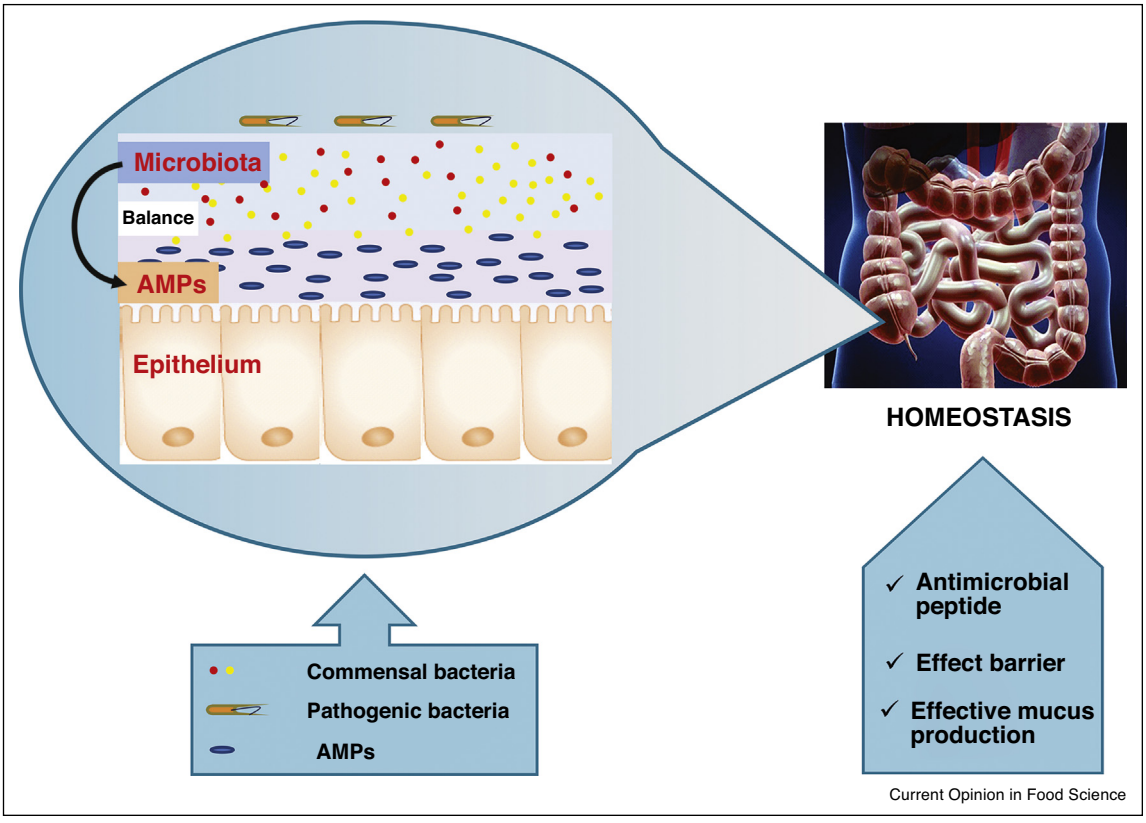
The gut microbiota composition

In the gastrointestinal tract in particular, the colon is the main site of microbial colonization, containing an estimated amount of 1.5 kg of microbes. The composition of the intestinal microbiota varies among the gastrointestinal tract [3]. Bacterial composition and distribution are determined by nutrient requirements [4,5]. The exact composition of the gut microbiota is still unknown, whereas advances in metagenomics technologies have recently begun to reveal that 90% of the bacterial phylotypes are members of two phyla Bacteroidetes and Firmicutes, followed by Actinobacteria and Proteobacteria [6] and that the majority of the dominant bacterial species observed in the fecal microbiota of an individual (approximately 80%) are specific to this individual [7].

Commensal and pathogenic bacteria require similar ecological niches to colonize and proliferate in the intestine. However, long-standing interactions during our evolution have generated a homeostatic relationship [8]. Commensal bacteria prevent pathogen infection by altering host environmental conditions, which can inhibit the growth of certain intestinal pathogens [9] or block incoming pathogens by competitive exclusion [10••]. In this context, the major physiological function of the resident microbiota is to act as a microbial barrier against microbial pathogens. There are many mechanisms of immune response of the intestinal microbiota, such as regulation of interleukins, IL-12 production, determination of Th1 and Th2 responses, and production of antibacterial substances by resident gut microbiota, such as AMPs (Figure 1) [2].

AMPs are ribosomally-synthesized natural antibiotics produced by nearly all organisms, from bacteria to plants and animals [11•]. The composite of healthy microbiota appears to be a prerequisite for AMP production. *Bacteroides thetaiotaomicron* appears to be among the key individual species that drive this production. *B. thetaiotaomicron* has been shown to induce expression of the matrix metalloproteinase matrilysin from the Paneth cells, which subsequently cleaves pro-defensin to form an active defense [12]. While one of the main functions of AMPs is the regulation of the number and composition of intestinal microbiota, the interactions of AMPs and microbiota are bidirectional, as various microbial species as well as products of microbial metabolism have been shown to stimulate the production of different types of AMPs [9,11•].

Figure 1



The resident microbiota acting as a microbial barrier against microbial pathogens.

Antimicrobial peptides (AMPs): structure and mechanisms of action

The activity of AMPs in humans was demonstrated for the first time in the 1950s and 1960s with the observation that neutrophil's capacity in eliminating bacteria is associated with the presence of cationic proteins [11•]. Later, by the 1980s, insects and a wide variety of other animals were identified as AMP producers, using it as a protection strategy against pathogenic and invasive agents [13•].

Another important source of AMPs are dietary proteins such as milk, egg, fish, meat, algae or soy, which have already been reported. Processes that lead to bioactive peptide release include *in vivo* enzymatic digestion in the gastrointestinal tract both by human and microbiota enzymes, and *in vitro* food processing or ripening by starter cultures of microorganisms or by enzymes from animals, plants or microorganisms [14].

Natural AMPs have already been isolated and characterized in a wide range of species, from prokaryotes to humans [15•,16••]. The rise of multi-resistant bacteria and the crucial search for new antimicrobial agents have driven pioneering research on pharmacokinetics and the biological structures of peptide-based drugs. These compounds have a lower probability of multi-resistance [15•,11•,16••], as well as the ability to protect the host against a wide range of infectious agents such as bacteria, fungi, parasites, virus, and cancer cells [13•,16••,17].

The AMPs are defined as molecules with 12–60 amino acid residues, low molecular weight (between 0.7 and 9.0 kDa), high thermostability, positive charge, and an elevated presence of hydrophobic residues. The cationic force is probably the main characteristic that defines their selectivity by negatively-charged cytoplasmic membranes [13•,15•,18•], while their hydrophobicity would be responsible for the interactions of acil groups with fatty acids in the lipoprotein layer that includes bacterial cells [13•].

Structural diversity of AMPs

The structure–activity relationship (SAR) of AMPs is a key determinant because it provides information about the molecular mechanisms that regulate the AMPs' biological activity over pathogens [19]. Up until now, it has been understood that the antimicrobial capacity of many peptides is dependent on different biophysical properties that allow the adsorption, permeation, and rupture of microorganisms' cell walls [20••]. The main differences

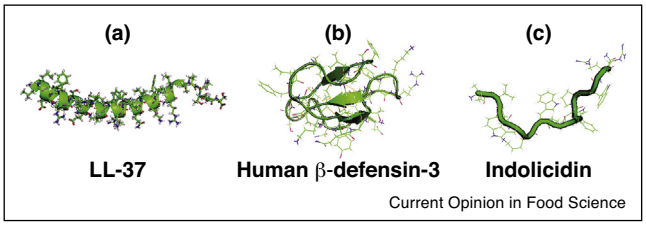
among AMPs are related to their low homology in amino acid sequences and their wide variety of secondary structures [18•]. Regarding structural/functional classification the AMPs aredivided into three main groups: amphipathic α-helical peptides, amphipathic β-sheet peptides, and extended peptides [21•,22].

Amphipathic α-helical peptides correspond to the major group of cationic AMPs. This group has the propensity to create alpha-helix folding (Figure 2a) in membranous environments, which increases their antimicrobial capacity promoting an agglomeration in the lipid–peptide interface occurs through intense electrostatic attraction with the anionic head of phospholipids. In Gram-negative bacteria, the attraction is related to high lipid concentration of phosphatidylglycerol (PG) and cardiolipin (CL), which present negative liquid charge in physiological pH. On the contrary, in the case of Gram-positive bacteria, the anions derive from teichoic and/or teichuronic acids [18•]. The most representative members of this group are cecropins, magainins, cathelicidins, and temporins [21•].

Amphipathic β-sheet peptides present a number of well-defined β-strand domains, generally without any helical domains (Figure 2b). In this group, the main representative members are β-hairpin and defensin. The contact with anionic membranes promotes peptide folding into transmembrane β-barrel oligomeric structures, but can also produce beta-sheet aggregates on the surface of cholesterol-rich membranes [13•]. A major part of the AMPs in this group are membrane-active with mechanisms based on the ionic interaction between cationic arginine residues and the cell membrane leading to the formation of toroidal pores [23]. However, evidence suggests that certain β-sheet peptides are capable of crossing the cell membrane and binding to DNA, interfering in DNA–protein interactions [21•].

Extended peptides have structural conformation defined by the presence of arginine (Arg), tryptophan (Trp), proline (Pro), cysteine (Cys), and histidine (His) that results in specific secondary structures (Figure 2c). Histatins, indolicidin, and PR-39 are representative members of this group [18•]. Generally, these peptides are not cell membrane-active, and their antimicrobial mechanism is attributed to the interaction with intracellular proteins that could inhibit the DNA replication process, for instance [13•,18•].

Figure 2



Secondary structure of representative AMPs in humans: **(a)** structure α-helical the human cathelicidin derived LL37 (PDB ID: 2K6O); **(b)** structure β-sheet of human β-defensin-3 (1KJ5); **(c)** structure extended of an indolicidin peptide (1G89). All images were generated using PyMOL (www.pymol.org).

Peptide mechanisms of action

The AMPs' action over invasive microbes occurs because of their membrane-interaction capacity or their ability to disturb or inhibit intracellular targets [15•]. Generally, the mechanisms related to cell death are grouped according to cell membrane dysfunction, intracellular function inhibition, and extracellular synthesis of biopolymers [11•].

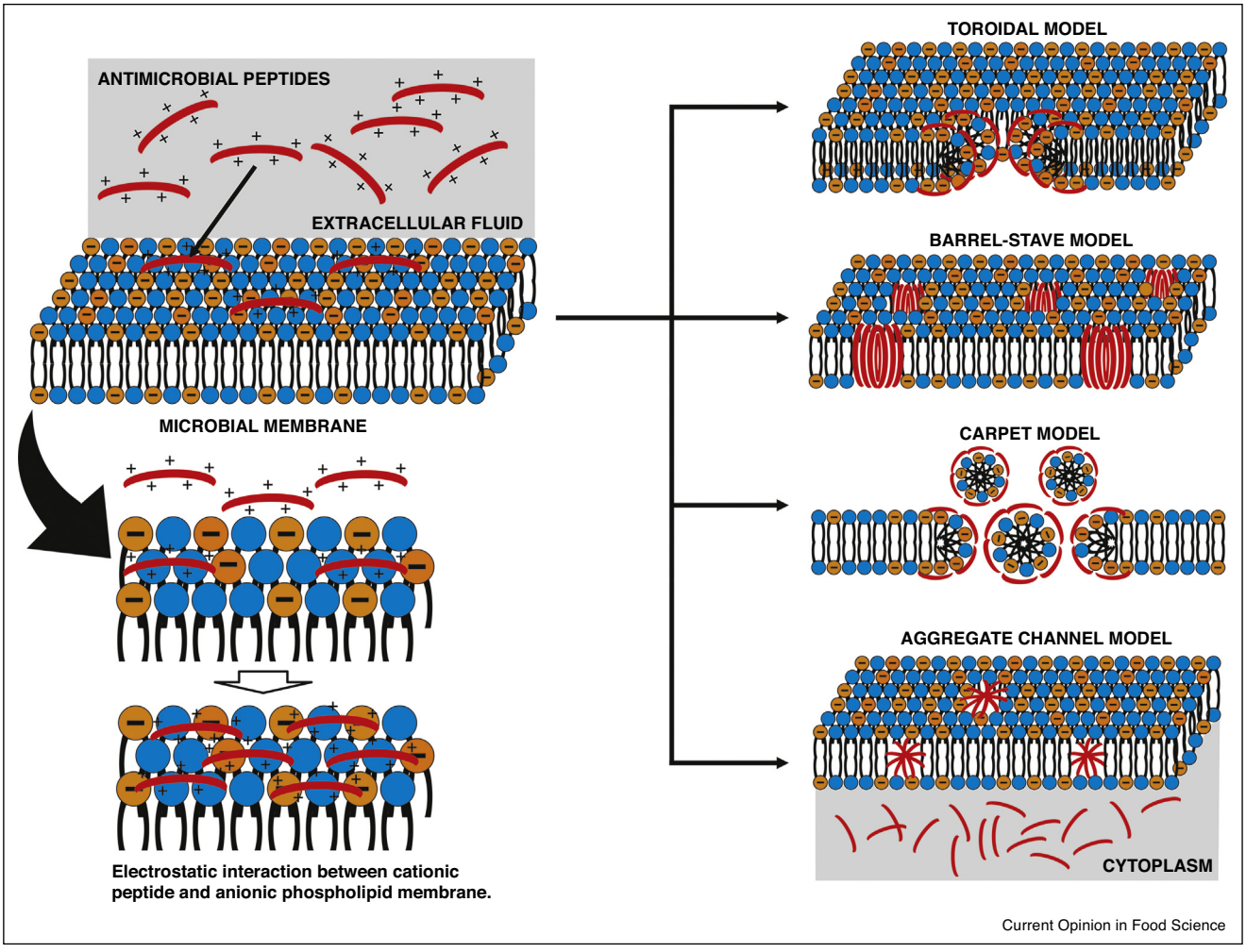
Membrane activity

Membrane activity consists of cell membrane permeabilization and is the main antimicrobial mechanism performed by AMPs [24]. Among the membranolytic activity mechanisms, the most cited are the toroidal model, barrel-stave model, and carpet model [18•]. *Toroidal model*: This model consists of continuous distortions at the lipid bilayer caused byelectrostatic attraction that cationic peptides promote over phosphate groups of the external and internal membrane surfaces. The association between peptides and lipids causes a partial loss in the positive liquid charge of AMPs that favors the peptide aggregates' formation in the membrane core resulting in its rupture and the consequent release of intracellular components [11•,15•]. *Barrel-stave model*: In this case, the transmembrane pore is formed by extremely hydrophobic AMPs, such as zervamicin. Peptides interact through their hydrophobic domains resulting in the formation of a helical beam structure, in which the hydrophilic side is composed of the internal pore coating, and the hydrophobic side interacts with the acil core of the membrane and achieves stability through van der Waals forces. The latter are deeply inserted into the acil membrane core promoting greater pore expansion and translocation of phospholipids to generate trans-negative electrochemical potential [25]. *Carpet model*: The carpet model consists of the rupture of the cell membrane due to the accumulation of peptides on its surface. The cationic AMPs are adsorbed by the cell membrane and remain electrostatically linked across diverse sites to anionic phospholipids' heads forming a carpet structure. This mechanism is based on detergent-like binding properties, where membrane disruption occurs despite formation of canals [11•,15•]. The peptide Pln149a, the human cathelicidin-derived LL37, and Xenopus alanine-substituted Magainin-2 amide are involved in this process [14]. The models described are depicted in Figure 3.

Non-membranolytic activity

Non-membranolytic activity occurs due to modification of membrane topology by some AMPs that reach intracellular targets using 'defects' or transient pores. After

Figure 3



Membranolytic and non membranolytic action mechanisms of AMPs.

cytoplasm permeation, the AMPs can affect DNA, RNA, chaperones, enzymes, and organelles like mitochondria. The primary model that represents non-membranolytic activity is the *aggregate channel model*. The main difference of this model is formation of short-term transmembrane aggregates instead of definitive pores or membrane rupture. The peptides bond to the anionic fraction of phospholipids attached to the cell membrane where non-structured aggregates are generated. This temporary configuration allows peptides to cross the membrane without significant depolarization and lamellar rupture occurring. This model is illustrated in Figure 3.

Cathelicidin and defensin: two major groups of human antimicrobial peptides

Previous studies have demonstrated that the host–microbiota relationship can overcome metabolic functions and form the host–microbiota–immune system. The immune system works along immune cells (neutrophils, macrophages, dendritic cells, *etc.*) and non-immune cells (epithelial lining of respiratory tract, gastrointestinal, and genitor urinary, fibroblasts and mesothelial cells) in order to generate positive responses against infectious agents [26]. These cells react to stimuli induced by invading agents and release a wide range of effector molecules such as cytokines, chemokines, antimicrobial peptides (AMPs), prostaglandins, free radicals, and bioactive amines that are capable of eliminating pathogenic bacteria, fungi, virus, and parasites [13•,27•,26]. The AMPs are the first line of defense of the human immune system because of direct antimicrobial functions and innate immune responses and/or adaptive against infectious agents [18•,26].

Defensins

The active structure consists of a triple β-sheet chain composed of 30 amino acid residues, in which six are conserved cysteine residues (Cys) responsible for

secondary structure stabilization and classification of α-, β- or θ-defensins. The α- and β-defensins are the most relevant for human health [16••,26,28].

Generally, defensins act on the microbial membrane surface to create pores that increase cellular permeability resulting in interruption of the electrochemical gradient [28]. These AMPs are expressed by neutrophils and by Paneth cells of the small intestine as inactive precursory proteins that are enabled following the action of specific proteases [29,30].

Cathelicidins

The only AMP of the cathelicidins family significant to human health is hCAP18/LL-37. This AMP is an inactive 18 kDa precursor that forms biologically-active LL-37 after exposure to extracellular serine-proteases [16••]. In humans, it is expressed in constitutive and/or inductive ways by immune system cells and epithelial cells acting like defensins by means of pore formation on the surface of microbial cells as a result of electrostatic attraction between LL-37 and phospholipidic membrane [28].

Gut microbiota regulate the production of defensins, cathelicidins, C-type lectins, ribonucleases, and S100 proteins in intestinal epithelial cells and Paneth cells, which rapidly kill or inactivate microorganisms [31]. Evidence shows that defensins and cathelicidins cooperate *in vivo* with a lot of other mediators in host defense, such as cytokines, chemokines, complements, acute-response proteins and other antimicrobial proteins, as well as cellular components to produce an orchestrated defense against invading pathogens [32]

Table 1 summarizes the main characteristics of human defensins and cathelicidins.

Table 1

Human defensins and cathelicidins: tissue expression and activity

AMP family	Subgroups	Tissue expression	Activity
Defensins α-Defensins	HNP-1 HNP-2 HNP-3 HNP-4 Paneth cell defensins HD-5 HD-6	Phagocytic cells (neutrophils, NK cells, monocytes/macrophages, T and B cells), bone marrow, respiratory tract Special epithelial cells of GI tract. HD-5 is also found in kidney and male e female reproductive tract	Antimicrobial - HNP-1,2 (*S. aureus*, *P. aeruginosa* and *E. coli*); - HNP-(1–3) (anti HIV); - HD-5 (*L. monocytogenes*, *E. coli*, *S. typhimurium*, *C. albicans*, *C. difficile*, HPV, HIV, influenza virus); Immunological - Chemotaxis: HNP-(1–3) chemotactic (monocyte); - Degranulates mast cells. Regulates complement activation. Inhibits binding of LPS to LBP. Immuno-adjuvant function. Increases antigen mediated cellular and humoral immunity.
β-Defensins	HBD-1 HBD-2 HBD-3 HBD-4	Majorly expressed in GI tract, airway epithelium, genitourinary epithelium, but also found in human plasma, kidney, prostrate, uterus and thymus Intestinal epithelium as well as trachea, oral and nasal mucosa, skin, eyes, salivary glands, urinary tract, multiple leukocytes such as monocytes, macrophages and dendritic cells as well as in NK cells and T-cell population Oral mucosa, gastric antrium lung, epidydimis	Antimicrobial - HBD-1 (*C. albicans*, *B. fragilis*, *E. faecalis* and *E. coli*); - HBD-2 (Bactericidal for *P. aeruginosa*, *E. coli* and *C. albicans*, but bacteriostatic towards *S. aureus*); - HBD-3 (*E. coli*, *S. aureus*, *P. aeruginosa*, *S. pyogenes*, *Enterococcus faecium* vancomycin resistant, *P. gingivalis*, *C. albicans*, *etc*.); Immunological - Chemotaxis: HBD-2 (mast cells, immature DC) and HBD-3 chemotactic (monocyte, macrophage, immature DC). Mast cell degranulation, immune adjuvant effect, prostaglandlin 2 production, promotes tumor antigen mediated cellular and humoral immunity. Antimicrobial *E. coli* BL21, *S. cerevisiae*, *S. aureus*, *S. pneumonia*, *Burkholderia cepacia*, *P. aeruginosa*.
Cathelicidins	LL-37	Minimal expression in small intestine, abundantly expressed in differentiated epithelium of the colon, keratinocytes, airway epithelium, myeloid cells, bone marrow, thymus, liver, spleen and pancreas	Antimicrobial - Gram positive and Gram negative bacteria (*E. coli*, *K. pneumonia*, *P. aeruginosa*, *Neisseria gonorrhoeae* and *Streptococcus* sp.), gastrointestinal infections (*Helicobacter*, *Shigella* sp., *Salmonella* sp. and *C. albicans*), oral microorganisms, (*Streptococcus mutans*, *Porphyromonas gingivalis*, and *A. actinomycetemcomitan*), fungi, parasite andenveloped virus. Immunological - Chemotaxis: (neutrophils, blood monocytes, CD4+T cells); - Antiendotoxic, angiogenic, skin reepithelialisation, release of histamine from mast cells.

Adapted from: Dutta and Das [26].

Conclusions

It has recently been found that intestinal mucosa play a role in diverse mechanisms, besides acting as a passive barrier. One of the strategies utilized by hosts threatened by pathogenic invaders is to initiate the expression of molecules such as cytokines, chemokines, and antimicrobial peptides via epithelial and immune cells. AMPs have been the focus of recent studies because of their wide range of action and lower probability of developing bacterial resistance.

The AMPS can be delivered by analogous molecules or foods, but the major challenge is to isolate and purify the peptides with bioactive potential, maintaining their activity and effect after gastrointestinal digestion without influencing the commensal microbiota. In addition, the use of AMPS as a drug or functional ingredient should be addressed with the following considerations: what is the best approach to AMP administration? How can the functionality of AMPs be guaranteed in the intestinal tract? What is the influence of AMPs over the commensal intestinal microbiota? Finally, many aspects are yet to be fully studied and validated before AMPs can be considered an effective health promoter.

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