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[Margarita Saubenova](#), [Alexander Rapoport](#)^{*}, [Zhanerke Yermekbay](#), [Yelena Oleinikova](#)^{*}

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Review

Antimicrobial Peptides, Their Production, and Potential in the Fight Against Antibiotic-Resistant Pathogens

Margarita Saubenova ¹, Alexander Rapoport ^{2,*}, Zhanerke Yermekbay ¹ and Yelena Oleinikova ^{1,*}

¹ Research and Production Center of Microbiology and Virology, Bogenbay Batyr str., 105, Almaty, 050010, Kazakhstan

² Laboratory of Cell Biology, Institute of Microbiology and Biotechnology, University of Latvia, Jelgavas Str., 1-537, Riga, LV-1004, Latvia

* Correspondence: rapoport@mail.eunet.lv (A.R.); elena.olejnikova@mail.ru (Y.O.)

Abstract: The article reviews the literature on antimicrobial peptides (AMPs) that exhibit unique antimicrobial mechanisms, such as broad-spectrum activity, low development of antimicrobial resistance, and the ability to modulate the immune response of the host organism. Information is provided on the significant potential of AMPs in the fight against pathogens threatening human health and food safety. Enrichment of the human diet with biologically active peptides obtained using the proteolytic activity of lactic acid bacteria (LAB) is proposed as a simple, accessible, and viable alternative to antibiotics that does not have a harmful side effect. The review briefly covers the methods for obtaining AMPs and features of the LAB proteolytic system responsible for producing bioactive peptides in the environment. It has been shown that using various LAB strains makes it possible to produce high-quality whey-based beverages with different directions of antagonistic activity against opportunistic pathogens and helps optimize the gastrointestinal microbiota. It is assumed that such drinks can reduce the dose of antimicrobials in combined therapy of various infectious diseases and be a preventive measure against contagion and the spread of antimicrobial resistance.

Keywords: antimicrobial peptides; antagonistic activity; antimicrobial resistance; biofilm; proteolytic enzyme; lactic acid bacteria

1. Introduction

The rapid growth of antimicrobial resistance has become one of the major challenges in modern healthcare, complicating disease control and threatening advances in general surgery. WHO warns that antibiotic resistance to pathogens could become the leading cause of global deaths by 2050 [1]. The progressive emergence of multidrug-resistant bacteria and the decline in the effectiveness of antibiotics necessitate the identification of new drug classes, their pharmaceutical forms, and the development of alternative antimicrobial therapy strategies [2]. As disillusionment with the effectiveness of antibiotics increases and their production declines, the number of pathogens resistant to existing drugs rapidly increases worldwide [3].

The most promising and ecologically sound approach to solving this problem is to exploit the principle of the human innate immune system, namely the synthesis of antimicrobial peptides (AMPs) with a broad spectrum of antagonistic activity destroying invading microorganisms [4,5]. AMPs are polypeptide sequences of 5 to 100 (most frequently 12–50) cationic and hydrophobic amino acids with direct antimicrobial activity. They are currently considered a prospect for developing new antibiotics [6,7]. The number of AMPs is large and diverse. Many of them, in addition to antimicrobial properties, have immunomodulatory, anticancer, antibiofilm, and other beneficial functions [8], which allowed them to be called host defense peptides [9–11].

This discovery has already moved beyond the traditional focus on peptides of human origin to include a wider range of structures identified in other natural sources or obtained by medicinal chemistry. Bioactive peptides derived from animal and plant proteins have recently attracted considerable attention due to their multifaceted health benefits [12–15], especially since they have not shown any serious side effects as components of foods safely consumed by humans for many years. The strength of peptides as drug candidates is their sufficient efficacy, specificity, and high safety profile. However, further studies are needed to determine the relationship between their various physicochemical properties and interactions with other antimicrobial drugs for the widespread use of AMPs.

The origin of AMPs, their classification, biological characteristics, mechanisms of their action, clinical application in infectious diseases of humans and animals, use in the food industry, as well as in plant protection and aquaculture, are currently receiving much attention [5,16–19].

2. Antibiotic Peptide

More than three thousand AMPs of natural origin have been identified. They are produced by various organisms occupying almost all steps of the evolutionary ladder from prokaryotes to humans. Peptides regulate gene expression and protein synthesis in all living organisms. 78.29% of currently known natural AMPs are of animal origin (with AMPs from amphibians and arthropods being the most common), 12.17% bacterial, and 7.95% of plant origin (Antimicrobial Peptide Database). AMPs are part of innate immunity [16,20,21] and are present in both eukaryotes and prokaryotes. They differ in the number of amino acids, the distance between them, the total charge, solubility, and other physicochemical properties, as well as in the mechanism of action.

AMPs show antagonistic activity against all types of pathological microorganisms (archaea, bacteria, fungi, and protozoa) without side effects and contribute to developing their resistance to a much lesser extent than conventional antibiotics [22]. Most of the AMPs are antibacterial peptides that have a broad inhibitory effect on common pathogenic bacteria both in clinical medicine and in food products. Many AMPs have shown low cytotoxicity and good antagonistic activity against gram-positive and gram-negative bacteria. At the same time, some AMPs of natural and artificial origin can inhibit pathogenic fungi such as *Aspergillus* and *Candida albicans* [23], which are common in clinical medicine, food, and agriculture. Several AMPs have shown the potential to combat COVID-19 by inhibiting the spread of the viral infection in various ways [24–26].

AMPs can also regulate pro-inflammatory responses, promote cell proliferation, alter gene expression, and kill cancer cells, participating in the immune regulation of inflammatory diseases and respiratory, skin, and soft tissue infections [27,28]. In addition to their antimicrobial effects, they modulate inflammatory and immune responses and promote wound healing [27,29]. The efficacy of AMPs is regulated by factors such as net charge, hydrophobicity, and the ability to form amphipathic secondary structures [30]. When properly balanced, these characteristics allow AMPs to selectively target bacterial membranes without damaging eukaryotic cells. The secondary structure of AMPs varies and typically includes alpha helix and beta-sheets, as well as extended coils and their combinations [7,16,31]. Most often, AMPs are characterized by a positive charge, which allows them to react with negatively charged membranes of target cells.

The membrane-associated mechanism of action is the main one for AMPs [30], only a few peptides affect intracellular factors. There are several main mechanisms of membrane damage by peptides [13,31]. AMPs can form barrel-stave pores, inserting vertically into the target plasma membrane and forming transmembrane pores. With the carpet mechanism, the absorption of peptides parallel to the lipid bilayer ruptures the cytoplasmic membrane. When these two mechanisms are combined, toroidal pores are made. It is also possible to form disordered toroidal pores with the participation of a smaller number of peptides and stabilization of the membrane opening by other peptides. An aggregate or detergent-like model is also distinguished, in which aggregates are formed between peptides and membrane lipids producing a peptide-lipid complex micelle and channels through which the contents of the cell flow out [16,32].

Other mechanisms include non-membrane targeting and immune modulation [13]. Short peptides consisting of 2–7 amino acid residues can penetrate the nuclei and nucleoli of cells and interact with the nucleosome, histone proteins, as well as with both single-stranded and double-stranded DNA, regulating their methylation status, which is an epigenetic mechanism of gene activation or repression, both in the normal state and in cases of pathology and aging. It is assumed that short peptides were evolutionarily among the first signaling molecules regulating matrix-directed synthesis reactions that expand the prospects for developing effective and safe drugs based on short peptides, including antimicrobial and antiviral drugs [33].

Various modifications, including amino acid substitutions, peptide tagging, or lipid conjugation, can either improve or worsen the efficacy of AMPs. Notably, sometimes a slight decrease in charge, hydrophobicity, or structural stability improves the overall therapeutic potential of AMPs. Understanding these complex interactions is key to developing AMPs with greater antimicrobial activity and less toxicity, making them promising candidates for treating antibiotic-resistant bacteria [34]. Thus, collecting the most relevant information will help to design and select the most effective AMPs [35].

As the demand for peptide-based therapeutics grows, so does the need for sustainable and eco-friendly synthetic methods. Traditional peptide synthesis, although efficient, often involves environmentally depleting processes that produce significant waste and consume vast resources. Integrating green chemistry offers sustainable alternatives by prioritizing green processes, waste reduction, and energy conservation [36]. Synthetic antimicrobial peptide mimics are a promising class of novel antibiotics designed to retain the antimicrobial pharmacophore while providing the flexibility of chemical structure to tailor desired properties such as improved activity, reduced cytotoxicity, and proteolysis, with the advantage of financial viability [37]. The main types of AMPs (including polyamino acids, short AMPs, and lipopeptides) and factors to optimize their antimicrobial effects are explored. The latest developments in AMP application are summarized, including antimicrobial agents, wound healing, preservatives, antibacterial coating, and other problems in improving antibacterial peptides, as well as the development prospects in this field [18].

3. Using AMPs to Combat Antibiotic-Resistant Pathogen

AMPs contribute much less to developing resistance than conventional antibiotics, without showing side effects [22]. The AMP-based treatment strategy has great potential in combating infections caused by drug-resistant bacteria, which pose an ever-growing threat to human health.

Antibiotic resistance and the associated occurrence of chronic diseases are dramatically increased by the formation of bacterial biofilms, which is one of the main threats to modern medicine. AMPs are a very encouraging potential replacement for traditional antibiotics [38,39]. Almost all medical device-associated infections exist in the form of biofilms [40]. Extracellular polymeric substances that protect bacteria in biofilms enable them to develop a high level of resistance to both the host immune system and the antibiotic. This reduces the effectiveness of treatment, causes its chronic course, and requires developing a strategy to counteract the formation of films and destroy existing ones [41–43]. The ability of AMPs to penetrate established biofilms has been shown [44], and the possibility of their use as an effective means to combat various chronic infections associated with biofilms has been reported [45,46]. The main types of AMPs with a wide range of targets, including viruses, bacteria, fungi, and parasites, their modes of action, and common mechanisms of resistance to them, as well as the principles of creating effective drugs based on them, including the potential for their use in the control of biofilms and persistent cells, are in the spotlight [47].

AMPs are promising candidates for developing new antibiofilm drugs because they can act at different stages of biofilm formation, on various molecular targets, and with diverse mechanisms of action. They can inhibit biofilm formation and adhesion, suppress quorum sensing factors, and disrupt already-formed biofilms [48]. AMPs have promising broad-spectrum activity against Gram-positive and Gram-negative bacteria in biofilms [49]. It has been shown that the antimicrobial activity of peptides against biofilms formed by Gram-positive microorganisms can be significantly higher

than that of traditional antimicrobial drugs [50], and therefore the mechanism of action of AMPs and their antibiofilm activity are being actively studied [51–53].

The use of AMPs that act on the bacterial cell wall facilitates the access of the antibiotic to its intracellular target, which allows to reduce its effective concentration. Therapy with the simultaneous use of antibiotics and AMPs helps to reduce antibiotic resistance and can be expected to alleviate toxicity and adverse side effects [54–59]. Antibiotic adjuvant restores antibiotic activity and extends its lifespan, representing a more productive, timely, and cost-effective strategy to combat drug-resistant pathogens.

Natural and synthetic AMPs are considered to be next-generation antibacterial agents. In addition to their direct antimicrobial action, increasing evidence shows that some AMPs effectively enhance the activity of conventional antibiotics and can be used as adjuvants. Combinations of AMPs and antibiotics demonstrate an improved therapeutic effect against antibiotic-resistant bacterial infections and minimize the emergence of resistance. Providing a synergistic action, AMPs become ideal candidates for combination therapy with traditional chemical antibiotics. They can facilitate the penetration of antibiotics through the exopolysaccharide layer of biofilm communities of microorganisms or even prevent bacterial adhesion and biofilm growth, significantly reducing the effective concentration of the antibiotic, blocking the emergence of bacterial resistance mechanisms, or interfering with the community quorum sensing systems. At the same time, effective concentrations of peptides for adjuvant activity and suppression of bacterial resistance are significantly lower than those required for direct antimicrobial action. Moreover, combinations of AMPs and antibiotics are much less likely to promote the development of resistance and the transfer of cross-resistance [4,60,61]. This creates the basis for using AMPs in new combination chemotherapeutic drugs [62].

As the growing problem of antimicrobial resistance requires new strategies to combat this global public health threat, conjugates consisting of a membrane-active peptide, called a “vector,” capable of delivering cargo across the bacterial outer membrane, attached to either a current or new antibiotic, called a “cargo” or “payload,” are being developed [63].

Strategies and methods for de novo creating potentially active AMPs with increased antibiofilm efficacy are also discussed [64]. It is assumed that the reduction in bacterial adhesion to surfaces and biofilm growth is due to the ability of the peptide to coat either the surface of the biomaterial or the bacteria themselves. Degradation of formed biofilms by bactericidal and non-bactericidal peptides within 1 h after incubation occurs due to the destruction of embedded bacteria or the separation of living ones. These data not only shed light on the mechanism of inhibition and degradation of biofilms but may also help to develop antibiofilm AMPs [65]. In the case of *Pseudomonas aeruginosa*, a common pathogen of nosocomial acute and systemic infections with multiple drug resistance, the therapeutic effect is associated with the destruction of the membrane structure due to interaction with lipopolysaccharides, an increase in the level of reactive oxygen species, or the influence on cellular components leading to cell lysis [66]. Using *Pseudomonas fluorescens* as an example, it was shown that the antimicrobial activity of the peptide nisin was increased when used synergistically with ampicillin [67].

Due to their high biological efficacy, AMPs have already found their place in antibiotic replacement programs to combat bacteria with serious drug resistance. Various strategies are used to develop and biosynthesize optimized AMPs with improved bioactivity and productivity while reducing toxicity and cost [68].

The therapeutic value of AMPs lies not only in their increased efficacy, high specificity, reduced drug interactions, low toxicity, biological diversity, and direct action properties in the treatment of infectious diseases but mainly in the inability of pathogens of various taxonomic affiliations to develop resistance to most of them. Combining various AMPs with enzymes hydrolyzing signal molecules of the resistance mechanism of different microorganisms (quorum sensing) is one of the leading approaches to obtaining effective antimicrobial drugs and solving the problem of antimicrobial resistance. In the study by Aslanli et al. [69] the most suitable combination was selected,

which contributed to stabilizing enzymatic activity against various microorganisms (bacteria and yeast), higher than that of AMPs without enzyme.

AMPs have emerged as a promising alternative due to their specific mode of action, broad spectrum, and difficulties developing resistance by microbes. Currently, AMPs such as bacitracin, gramicidin, polymyxins, and daptomycin are used in clinical practice. To make AMPs more drug-active, their cytotoxicity should be reduced while increasing their efficacy and proteolytic stability [70]. There is evidence of the influence of peptide length and helicity on its toxicity [47], which can be used in practical work. New technologies such as modifying their amino acid structure and using different delivery methods are being integrated into developing AMPs [71].

4. Using AMPs for Human Health

In recent years, increasing attention has been paid to the human microbiome, its relationships with infectious disease pathogens, and the potential to exploit this complex ecosystem to develop new treatment strategies [72].

It is known that various human diseases are associated with changes in the structure and function of the microbiota. These changes can be mediated by AMPs produced by the host and its microbiota, which play a crucial role in the co-evolution of host bacteria [73]. Homeostasis of the microbiota is also largely associated with AMPs from food. Peptides are present in almost all foods, but most often in protein-rich foods of animal and plant origin. One of the most important sources of natural bioactive peptides is milk, the protein fractions of which (caseins and whey proteins) during fermentation with lactic acid bacteria (LAB), as well as during gastrointestinal digestion or the use of proteolytic enzyme preparations, serve as a source of natural bioactive peptides that have a very beneficial effect on human health [74,75].

Dietary bioactive peptides have a positive effect on gastrointestinal homeostasis by modulating barrier function, immune responses, and intestinal microbiota, however, clinical data on their safety and efficacy are still insufficient, and further research is needed to justify their use in regulating intestinal health and function [76].

Regardless of the LAB strain, the peptides obtained with their help primarily have antimicrobial activity manifested through various mechanisms [77]. They regulate intestinal microbiota directly inhibiting pathogenic microorganisms and promoting the growth of beneficial bacteria.

Spoilage of food, feed, and various crops due to the development of mold, which can reduce the quantity and quality of manufactured products and even destroy them, is the cause of significant economic losses. Mycotoxins produced by mold fungi cause poisoning, sometimes with a fatal outcome. The widespread distribution of mycotoxigenic fungi is facilitated by their ability to colonize various substrates, as well as the lack of effective control measures [78]. The widespread use of chemical preservatives requires the development of alternative ways to preserve manufactured products due to the growing consumer awareness of their possible harm to health.

The immunocompromised patients, including those who have undergone organ transplants or chemotherapy, are at increased risk of fungal infections. The number of clinically available antifungal drugs is limited, as some of them are toxic and have serious side effects. Their action against pathogenic yeasts is only fungistatic [79]. A high potential for combating toxigenic fungi, combined with harmlessness to the human body, as shown by centuries of practice, is the use of LAB - potential sources of secondary metabolites, such as organic acids and bacteriocins, and, most importantly, peptides with high antifungal activity [80–83], affecting both the membranes of fungal cells [84], and, like antibiotics, on intracellular targets [85]. LAB that inhibit the growth of pathogenic microorganisms in food are a viable alternative to chemical preservatives due to their qualified presumption of safety (GRAS status) [86].

Nowadays, food safety is becoming an increasingly important international issue. The growing demand for harmless natural preservatives has contributed to developing an intensive field of research on bacteriocins produced by LAB as a new spectrum of antimicrobial compounds for effective control of food pathogens without serious side effects. To prevent the development of resistance to them, various mechanisms of resistance developed by food pathogens are being

investigated [87]. Further research in this direction will expand the understanding of their mechanism of action and determine specific conditions for increasing their stability and applicability in food preservation [88].

Toxigenic fungi greatly threaten food safety. Studies of goat whey hydrolysate containing 27 peptides showed that when added to the dough, it exhibits high antagonistic activity against 10 toxigenic fungi of the genus *Penicillium*, inhibiting their growth and the production of mycotoxins in bread by 85-100%, thereby extending its shelf life [89].

Broad-spectrum AMPs of dairy origin are of increasing interest as an attractive and safe additive to extend the shelf life of minimally processed foods, as a viable and sustainable alternative to conventional food preservatives [90], which can be incorporated into the food matrix without compromising consumer health, while contributing to the creation of added value in the resulting products. The positive feature of AMPs is their biocompatibility and biodegradability, thermal stability, and high selectivity, which is also very attractive for food preservation [88]. Importantly, unlike antibiotics, peptides are completely broken down in the body, without showing negative consequences. In practice, one of them, namely nisin, isolated from the bacterium *Lactococcus lactis* [91], is already used commercially (as E234). Consumer demand for food products without chemical preservatives has stimulated the search for natural antimicrobials with a broad antimicrobial spectrum and improved properties.

5. Production of Bioactive Peptides

Plant and animal proteins are mainly used to obtain bioactive peptides [92]. The most effective methods for biotechnological production of peptides are enzymatic hydrolysis and microbial fermentation of proteins [19].

Proteolytic enzymes (proteases and peptidases) used to obtain peptides degrade proteins by hydrolyzing peptide bonds and belong to the group of hydrolases [93,94]. Depending on the place of cleavage of the peptide chain, proteases are divided into exopeptidases and endopeptidases, acting respectively on the terminal or internal peptide bonds of the peptide chain. In this case, aminopeptidases cleave one to three amino acids from the free N-terminal of the polypeptide chain, and carboxypeptidases act on the C-terminal of the polypeptide chain. The functional groups of proteases can contain different groups in the active site and are divided into serine proteases, cysteine proteases, aspartyl proteases, and metalloproteases [93,95,96]. Proteolytic enzymes can be obtained from plants, animals, and microorganisms. However, microbial enzymes are the most convenient to produce due to their greater stability, relatively simple nutritional requirements, rapid production process, and the possibility of its standardization. Industrially produced proteolytic enzymes are produced by LAB, microorganisms of the genus *Bacillus*, and fungal microorganisms (yeasts and fungi of the genera *Aspergillus*, *Rhizopus*, and *Mucor*) [93] (Figure 1).

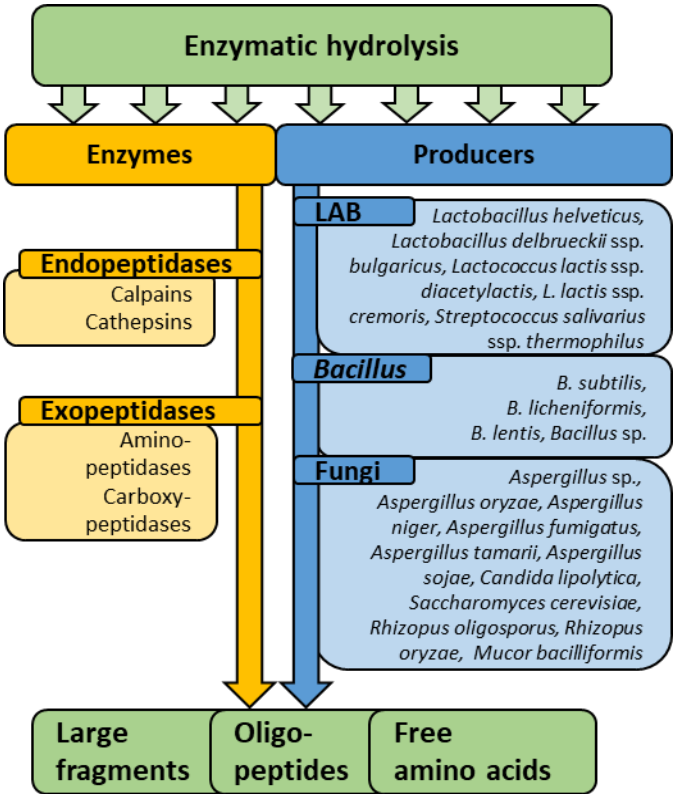


Figure 1. Receiving of bioactive peptides with enzymatic hydrolysis.

Microbial proteases exhibit the highest activity in a certain pH range. Alkaline proteases (pH range of 8–13) are most often used in the detergent and leather industries [97]. They are also widely used in the food industry for tenderizing and improving meat tenderness, obtaining meat hydrolysates, blood decolorization, and soy sauce and product preparation. Neutral proteases, active within neutral, slightly acidic, and slightly alkaline pH values, are also used to improve meat tenderness and dough preparation. Alkaline and neutral proteases are mainly produced by fungal and bacillary microorganisms [97]. Acid proteases (pH 2–6) are produced by LAB and fungi and applied in the food industry for degrading milk and whey proteins, wheat gluten, and fruit juice proteins.

Microbial fermentation is a more economical and cost-effective method for AMPs production. The microbial conversion of various protein-containing substrates occurs via solid-state fermentation or submerged fermentation (Figure 2) depending on the available free water volume [98]. Peptidase-producing microorganisms such as filamentous fungi, yeasts, *Bacillus* species, and LAB are used to obtain bioactive peptides [99]. Due to their GRAS status, LAB are the preferred microorganisms for fermentation of food substrates. They are also widely known as producers of AMPs in food products. The ability of microorganisms to produce extracellular and cell surface peptidases [100] allows the fermentation of substrates to produce both AMPs for medicine and novel food and beverage products enriched with bioactive compounds. Although LAB assimilate the produced peptides for growth, a large amount of peptides remains and accumulates during fermentation. To date, six main types of cell-envelope proteases of LAB have been identified: PrtP (*Lacticaseibacillus paracasei* subsp. *paracasei*, *Lactococcus lactis* subsp. *cremoris*, and *L. lactis* subsp. *lactis*), PrtB (*Lactobacillus delbrueckii* subsp. *bulgaricus*), PrtH (*Lactobacillu helveticus*), PrtS (*Streptococcus thermophilus*), PrtR (*Lacticaseibacillus rhamnosus*), and PrtL (*Lactobacillu delbrueckii* subsp. *lactis*) [101]. The secondary structure of the cell-envelope proteases of LAB suggests the presence of several domains that perform different functions: N-terminal preprodome for secretion and activation, catalytic serine protease domain, insert modulating specificity domain, A and B large possibly regulatory middle domains, a helical spacer

domain, an attachment hydrophilic cell-wall spacer domain, and a cell-wall anchor domain [102,103]. However, different types of proteases do not necessarily include all of the listed domains.

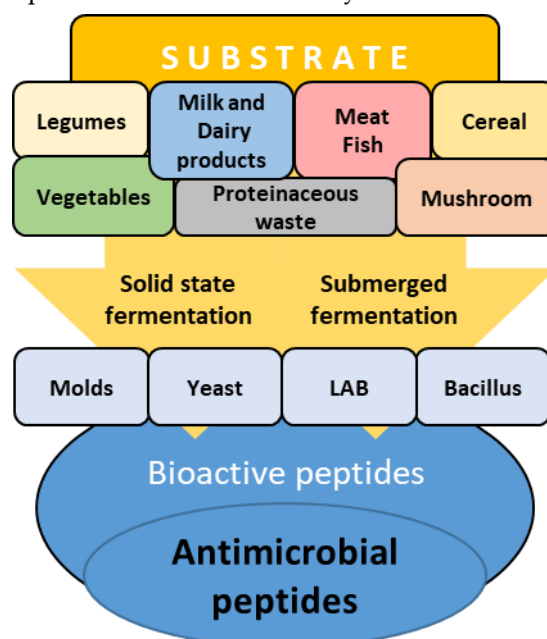


Figure 2. Sources and significance of milk and whey peptides.

Such species of LAB as *L. bulgaricus* and *L. helveticus* have a fairly powerful proteolytic system with a wide range of proteolytic enzymes [104]. Species of plant origin (*Lactiplantibacillus plantarum*, *Leuconostoc mesenteroides*, etc.) produce fewer proteolytic enzymes, living in an ecological niche richer in fibers than proteins. Therefore, dairy products and inhabiting them LAB are the best candidates for obtaining biologically active peptides.

6. Whey as a Raw Material for the Production of AMPs

The production of various cheeses, curds, and other dairy products, which are in ever-growing global demand, generates billions of liters of whey annually worldwide [105]. Although it is considered a secondary or waste product and has an unappealing taste, whey is rich in nutrients including soluble proteins (beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin, lactoferrin, immunoglobulins) as well as lactose, vitamins, minerals, and fat [106,107]. Whey proteins have a high biological value, exceeding that of egg white, and are a rich source of essential amino acids (branched-chain amino acids such as leucine, isoleucine, and valine, sulfur-containing amino acids cysteine and methionine, which enhance immune functions through their intracellular conversion to glutathione [107–109]. Providing an abundant supply of essential amino acids that stimulate organ and tissue regeneration mechanisms and help minimize immune suppression, whey is successfully used as an immunomodulator, antioxidant, anti-inflammatory, antidiabetic, anticancer agent [110]. Currently, whey is used as energy drinks for athletes and for therapeutic and prophylactic purposes in many countries around the world and is rightfully considered the energy source of the future.

Numerous studies have scientifically substantiated that functional products derived from whey provide a cascade of beneficial practical applications: in the prevention and/or adjunctive treatment of various lifestyle and aging-related diseases, promoting health and being effective in the treatment of numerous chronic diseases including diabetes, cancer, sarcopenia, liver disease, and cardiovascular diseases, as well as other immune-related chronic diseases [111,112].

Due to its composition, including a high water content, whey is the most promising raw material in the beverage industry [113–116], including the addition of other components that improve their biological and nutritional characteristics [117–119]. They are also promising for the production of biologically active substances, including AMPs [120,121], both in the form of pure preparations and in the form of drinks fortified with them [122–132].

Returning whey to the food chain in a palatable form is a hot topic in the literature [111,133]. The preparation of beverages from whole whey is not only the cheapest but also the most efficient method in terms of whey valorization. Whey and its components are increasingly being used to formulate new and creative beverages as a functional and dietary component in a wide range of beverages, including those with nutraceutical properties. As the dairy and functional food market continues to evolve, whey-based beverages made with the addition of fruit juices, milk or milk permeates, and other sources are expected to become increasingly popular [134].

Whey, in addition to lactose, contains valuable protein fractions and minerals that create its energy value. Currently, due to its beneficial health effects, intensive efforts are being made to use whey in the formulation of soft drinks, high-protein drinks, and as an additive to soups and fruit juices. In order to eliminate taste defects, final product instability, scale up the process and increase the nutritional and biological value of the resulting beverages, studies are being conducted to modify and improve the fermentation strategy and techniques have been developed to improve the product quality and shelf life. Its nutritional potential imparted by probiotic bacteria, macro- and microelements and their derivatives is also discussed [116]. Modern technologies for the enzymatic processing of whey make it possible to obtain not only beverages but also other useful functional foods and animal feeds [135]. To produce beverages from acid whey, which is less favorable for valorization than sweet whey, LAB that actively grow on it are isolated and studied, as well as their proteolytic activity for the fermentation of its protein fractions to obtain peptides. They are of particular interest because they exhibit the ability to inhibit the growth and development of pathogenic microorganisms by synthesizing bacteriocins and other AMPs, which are promising for use in the fight against various pathogens in targeted therapy of different diseases [136–139], including those known to be antibiotic-resistant. Most attention has been paid to AMPs exhibiting antibiofilm activity [140–144], since biofilm formation is a major factor contributing to antibiotic tolerance with increased infection severity, incidence, treatment failure, and mortality [145]. Bacteriocins show promising potential in the field of medicine to improve human and animal health. They are effective against multidrug-resistant bacteria, possessing antiviral, antifungal, and antiprotozoal (antileishmanial) activity, and have also been successfully used to treat some ulcers and some types of cancer [146].

The staff of the food microbiology laboratory of the Research and Production Center of Microbiology and Virology have compiled consortia of lactic acid microorganisms that are successfully used to prepare beverages with one or another health benefit. Thus, beverage formulations have been developed that are antagonistically active against opportunistic bacteria, *Candida* yeasts, and mold fungi [147–150]. As a result of the studies, functional whey-based beverages [151,152] were proposed that actively affect the indigenous microbiota [153] and are promising for use as probiotic products [154,155]. Whey-based drinks, due to the content of probiotic microorganisms [117–119,124] with antimicrobial activity against several pathogens, can be used to correct microflora in dysbacteriosis and as dietary supplements in drug therapy for certain infectious diseases.

7. Current State and Prospects for the Development of Peptide Science

AMPs are generally recognized as having a huge potential in developing effective antimicrobial strategies for replacing traditional antibiotics. However, despite all their advantages in practical use, there is an urgent need to eliminate their inherent disadvantages. The main ones are the possible damage to eukaryotic cell membranes, the risk of hemolytic side effects, high production costs and technical problems, and insufficient activity. To solve these issues, new technologies are used, including artificial intelligence, which opens up new possibilities [156]. Clarifying the selectivity mechanisms exhibited by AMPs when interacting with the membranes of the target organism would help to approach the development of methods for reducing cytotoxicity and increasing antimicrobial activity.

Traditional natural resources are insufficient to meet the growing need for AMPs. A promising reservoir of new bioactive molecules with potential pharmacological properties is still unexplored

marine microorganisms, which, due to their inherent self-defense mechanisms and adaptation to harsh conditions, include a wide range of chemical compounds such as AMPs and polyketides. These molecules could be used to create new and unique structures for developing alternative antibiotics as effective anti-biofilm agents [157]. Marine actinobacteria are recognized as promising for the development as sources of new antibiotics and biofilm inhibitor molecules [158].

There is a need to find new AMPs that could serve as natural preservatives in food products or as functional ingredients with potential health benefits. Their source can be, for example, food by-products, in particular waste, the protein fragments of which are characterized by a short length, low molecular weight, a significant content of hydrophobic and basic amino acids, and a positive net charge [159].

To address the problem of combating infections, further production of synthetic AMPs using biotechnological tools and processes is very promising. Some have already been shown to meet the required demand and be much more effective than conventional bioactive peptides [160]. Research into imparting AMPs with a stronger and longer-lasting activity without exhibiting toxicity seems promising. AMPs have potential antimicrobial properties against Gram-positive and Gram-negative bacteria. *In silico* studies of these AMPs are useful for killing drug-resistant bacteria [161]. For example, unnatural amino acids can be used to create artificial AMPs with improved properties and this can guide future antimicrobial drug design considerations [162]. It is envisaged that synthetic AMP analogs designed with some modifications can overcome the stability, toxicity, and activity limitations of naturally occurring AMPs [163]. Thus, Zhang et al. [164] developed a series of short mirror-symmetric peptides, among which LWRRRRWWL-NH₂ was selected with a broad spectrum of antibacterial activity against standard and antibiotic-resistant bacteria. This peptide had a low tendency to develop microbial resistance and, having similar activity to polymyxin B and melittin, was much safer.

The major barrier to the commercialization of AMPs is pricing and reimbursement conditions for new antimicrobials [165]. To overcome these limitations, peptide engineering techniques and the development of cost-effective algorithms for predicting AMPs with minimal toxicity [166] have been used, and some of them have now reached the commercialization stage in several pharmaceutical industries [167].

Industrial production of peptide-based food ingredients requires overcoming several challenges in product development to achieve economically viable downstream processes. Hybrid strategies for biopharmaceutical use based on computational modeling combined with heuristics and mechanistic modeling. Some hybrid designs currently used in biopharma are proposed, based on computer modeling combined with heuristics and mechanistic modeling, which minimizes the labor-intensive and costly trial and error method. Applying cost-effective metrics on a laboratory scale can lead to optimal downstream processing of peptide-based bioactive food ingredients, including peptide release and stability, depending on several industrial process parameters. Some methods for enriching whey-derived peptides are also discussed, which have potential industrial applications [168].

The study of AMPs as specific protein fragments with improved penetration, low toxicity, and rapid clearance of their biological activity involves various methodologies from *in vitro* assays to *in silico* methods [169]. Computer modeling (*in silico*) can be a useful tool for low-cost prediction of peptide sequences and can help elucidate the relationship between peptide structure and function. Other *in silico* tools can simulate the degradation of protein or peptide sequences, which is useful for designing a targeted hydrolysis process to ensure that the sequence of a given peptide is not degraded during gastrointestinal digestion [170]. Using *in silico* methodology has opened a new era in AMPs research with a simplified identification process, reducing the cost of laboratory screening. Advanced machine learning models that are both predictive and interpretable have been developed specifically to identify potent AMPs targeting WHO high-priority pathogens. The robustness of this approach allows for the accelerated development of new AMPs, offering robust countermeasures to antibiotic resistance [171].

In recent years, AMPs have been considered as a promising alternative to meet consumer demand for the production of safe, minimally processed, chemical-free, ready-to-eat food products with a long shelf life without losing fresh taste.

Due to the diversity of structures and functions, a wide spectrum of antifungal activity, high stability, and the possibility of biotechnological production of AMPs, their use in the food industry and agriculture is currently being considered to combat toxigenic fungi and mycotoxin biosynthesis, due to their ability to inhibit the enzymatic components of their biosynthetic pathways [172]. However, before they can fully replace antimicrobials in food production, difficulties associated with standardization and manufacturing on a commercial scale need to be overcome [173].

The use of AMPs in food preservation offers the potential to reduce food spoilage losses and the use of chemical preservatives, as well as to develop health-promoting food additives. The potential of some AMPs to inhibit foodborne pathogens is increasingly being studied in various food products (including dairy products, meat, fruits, and beverages) and taken into account in the development of nutraceuticals and pharmaceutical products containing foodborne AMPs. In the paper by Ahmed & Hammami [174], addressing these issues, an overview of the structural classification and antimicrobial mechanisms of action of AMPs is provided, and future trends in their use in food and pharmaceutical applications are discussed.

Research in this direction should be considered not only as a strategy to reduce food waste but also as an opportunity to improve food security and public health. AMPs are produced by many LAB during fermentation of not only milk and whey but also other food products

The most promising combination strategies to enhance the therapeutic potential of AMPs in combination with conventional antibiotics, extracellular matrix disaggregating compounds, biofilm signaling pathway inhibitors, and other peptide-based molecules are being investigated [175–177]. Microbial metabolites such as biosurfactants, AMPs, enzymes, and bioactive compounds have been identified as promising broad-spectrum antibiofilm agents [178], with peptides being evaluated as the most potent antibiofilm agents [179]. Thus, the peptide-based approach becomes a promising alternative for effectively combating the notorious resistant biofilms.

8. Conclusions

In recent years, it has been shown that it is possible to increase the effectiveness of traditional therapy for various infectious diseases and reduce the risk of drug resistance and side effects from treatment by combining conventional antibiotics with AMPs [167]. However, due to the practical unavailability of the latter due to some technical difficulties in obtaining, insufficient study, and high cost, their replacement with specially developed nutraceuticals and pharmaceutical products containing food-based AMPs seems more promising at this stage of society's development. It seems advisable to combine drug therapy with the simultaneous use of specially developed functional products, specifically, fermentation products, which have proven their high effectiveness in maintaining vital processes omitting undesirable side effects over many centuries of use in human practice. The most economically and environmentally justified in this regard should be recognized as whey-based beverages containing AMPs, which exhibit antagonistic activity against numerous agents of various diseases. The targeted production of a drink that suppresses the development of a particular pathogen is possible by selecting LAB that can produce the desired metabolites against each pathogen, which could replace mandatory antifungal drugs in treating bacterial infections. An example is whey-based drinks, which exhibit an antagonistic effect on *Candida* yeast, especially since using the existing antifungal arsenal against candidiasis is often limited by toxicity, drug interactions, and the high cost of some remedies [180]. Drinks of this kind can be developed as dietary beverages, including in children's groups, and regularly used due to their high biological value and harmlessness, protecting against the threat of infectious diseases or food poisoning.

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