fermentation

MDPI

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; msaubenova@mail.ru (M.S.); zhan98_14@mail.ru (Z.Y.)
[2] Laboratory of Cell Biology, Institute of Microbiology and Biotechnology, University of Latvia, Jelgavas Str., 1-537, LV-1004 Riga, 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 the 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

Academic Editor: Ronnie Willaert

Received: 17 December 2024
Revised: 10 January 2025
Accepted: 16 January 2025
Published: 17 January 2025

Citation: Saubenova, M.; Rapoport, A.; Yermekbay, Z.; Oleinikova, Y. Antimicrobial Peptides, Their Production, and Potential in the Fight Against Antibiotic-Resistant Pathogens. *Fermentation* **2025**, *11*, 36. https://doi.org/10.3390/fermentation11010036

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. The 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 (BAPs) 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. Overall, 78.29% of currently known natural AMPs are of animal origin (with AMPs from amphibians and arthropods being the most common), 12.17% of bacterial origin, 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. Thus, a novel antimicrobial peptide MOp2 from *Moringa oleifera* seed protein hydrolysates (His–Val–Leu–Asp–Thr–Pro–Leu–Leu) irreversibly damaged cell membranes of *Staphylococcus aureus* [23], while AMPs Lynronne 1, 2, 3, and P15s from the rumen microbiome killed clinical strains of *Pseudomonas aeruginosa* within 10 min to 4 h [24]. At the same time, some AMPs of natural and artificial origin can inhibit pathogenic fungi such as *Aspergillus* and *Candida albicans* [25], which are common in clinical medicine, food, and agriculture. Although the number of AMPs with antiviral activity is still limited, they already show great potential to become pharmaceutically available antiviral drugs. Such peptides can be derived from natural sources isolated from mammals and animal venoms or from artificial sources when bioinformatics tools are used [26]. A review by Ashaolu et al. [27] focuses on BAPs with inhibitory activity against human viruses, especially coronaviruses such as severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or SARS-nCOV19). It is shown that many biologically active peptides can inhibit various stages of the viral life cycle from pre-attachment to the release from infected host cells. In the work of Lee et al. [28], the data on antiviral peptides targeting viral membrane

envelopes were selected and rational approaches to their design were considered, taking into account the AMPs used for rational design.

SARS-CoV-2 variants continue to spread worldwide, causing waves of COVID-19 infections. In the search for effective antiviral drugs to combat them, the major protease (Mpro) of SARS-CoV-2 has been recognized as a promising therapeutic target due to its crucial role in viral replication and its persistence across variants. A natural antimicrobial peptide, Protegrin-2, with high binding affinity and stable interactions with allosteric residues of Mpro has been identified to inhibit the proteolytic cleavage activity of Mpro. Protegrin-2, as a potent inhibitor of Mpro, has potential for further drug development against COVID-19 infection [29] along with several other AMPs, inhibiting the spread of the viral infection in various ways. Another peptide, milk lactoferrin, has recently attracted much interest as a potent antimicrobial agent against several enveloped and naked viruses, such as rotavirus, enterovirus, and adenovirus [30].

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 [31,32]. In addition to their antimicrobial effects, they modulate inflammatory and immune responses and promote wound healing [31,33]. The efficacy of AMPs is regulated by factors such as net charge, hydrophobicity, and the ability to form amphipathic secondary structures [34]. 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 [7,16,35]. Most often, AMPs are characterized by a positive charge, which allows them to react with negatively charged membranes of target cells.

3. AMPs Mechanism of Action

The membrane-associated mechanism of action is the main one for AMPs [31]; only a few peptides affect intracellular factors. There are several main mechanisms of membrane damage by peptides [13,35]. 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 [16,36].

Other mechanisms include non-membrane targeting and immune modulation [13]. Short peptides consisting of two to seven amino acid residues can penetrate the nuclei and nucleoli of cells and interact with the nucleosome, histone proteins, and both single-stranded and double-stranded DNA, regulating their methylation status. This is an epigenetic mechanism of gene activation or repression both in the normal state and in cases of pathology and aging.

The mechanism of action of individual AMPs depends to a large extent on the type of target cell, peptide concentration, and physical properties of the bacterial membrane. During an infectious process, the action of peptides can be realized with the simultaneous participation of several mechanisms and their combinations, leading to membrane destruction and damage to one or several intracellular targets. A “group target” model of the mechanism of action has been proposed, according to which cationic AMPs with a high value of the total charge of the molecule bind to anionic molecules in the cytoplasm of

the microorganism, such as nucleic acids, enzymes with anionic surfaces, and block the processes in which these molecules participate [37]. It has been revealed that cationic peptides of different structural classes can inhibit the activity of enzymes containing an anionic binding site and participating in the transformation of aminoglycosides [38]. It has been shown that the rapid complex effect of AMP on bacteria and their extra- and intracellular targets makes it virtually impossible for resistance to develop to cationic peptides [39], which not only exhibit antimicrobial activity but also modulate the effect of endogenous bioregulators and protective functions of the body, opening up new ways and possibilities for treating diseases of various origins. Thus, cathelicidin peptides affect the proliferative activity of cells, initiating wound healing and re-epithelialization after skin damage by epidermal keratinocytes. The LCAP-18 peptide, the precursor of the LL-37 peptide, was shown to be produced in epidermis cells adjacent to the damaged skin area. When the wound heals and re-epithelialization is complete, the expression level of the LCAP-18 peptide decreases to the basal level. Two cathelicidins, human LL-37 peptide and mouse CRAMP peptide, have been found to induce angiogenesis, which is necessary for tissue repair and wound healing, as well as for the development of innate immune responses [40]. Thus, AMPs represent a promising basis for developing drugs that accelerate the healing of skin damage. This is especially important because the skin is the main barrier between the internal and external environment of the body and most often interacts with pathogenic microorganisms.

4. Optimization of AMPs Action

It is assumed that short peptides were evolutionarily among the first signaling molecules regulating matrix-directed synthesis reactions, which expands the prospects for developing effective and safe drugs based on short peptides, including antimicrobial and antiviral drugs [41].

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 [42]. Thus, collecting the most relevant information will help to design and select the most effective AMPs [43].

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 [44]. 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 [45]. 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].

5. 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.

The AMPs are very promising for further research and clinical application due to the undeniable need for new ways to combat infections and the important role of peptides in innate immunity. Peptides such as human Beta-Defesin-3 and Epinecidin-1 from *Epinephelus coioides* have shown in vitro efficacy against carbapenem-resistant *Klebsiella pneumoniae*, *Klebsiella aerogenes*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [46]. The AMPs Lynronne 1, 2, 3, and P15s from the rumen microbiome killed clinical strains of *Pseudomonas aeruginosa* within 10 min to 4 h [24].

In general, some of AMPs have already entered the world market and contributed to success in the treatment of various infections. At present, several AMPs are used in clinical practice. For example, the plectasin-derived peptide NZ2114 is a treatment for methicillin-resistant S. aureus (MRSA) infection [47] and the cyclic lipopeptide polymyxin B, a fermentation product of *Bacillus polymyxa*, is effective against resistant Gram-negative bacteria and is widely used to treat urinary tract infections, meningitis, otitis, periodontitis, lung infections, ears, eyes, and wound infections [48,49]. However, since polymyxin B has neurotoxic and nephrotoxic effects in high concentrations [50], the peptide is placed in lipid nanoparticles or liposomes to reduce side effects [51]. This contributes to a decrease in its minimum inhibitory concentrations and an increase in its antimicrobial effect. AMPs, such as Nisin and P10, inhibit extensively drug-resistant *Acinetobacter baumannii* isolates and colistin-resistant *Pseudomonas aeruginosa* at minimum inhibitory concentrations of 64–256 and 8–32 μg/mL for nisin and P10, respectively [52].

5.1. AMP for Suppression of Microbial Biofilms

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 [53,54]. Almost all medical device-associated infections exist in the form of biofilms [55]. 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 [56–58]. The ability of AMPs to penetrate established biofilms has been shown [59], and the possibility of their use as an effective means to combat various chronic infections associated with biofilms has been reported [60,61]. 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 [62].

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 [63]. AMPs have promising broad-spectrum activity against Gram-positive and Gram-negative bacteria in biofilms [64]. 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 [65], and therefore the mechanism of action of AMPs and their antibiofilm activity are being actively studied [66–68]. Thus, the metallo-antimicrobial peptide Gaduscidin-1 (Gad-1) has been shown to destroy established *P. aeruginosa* biofilms [69].

This peptide is characterized by a combined mechanism of action, including the ability to cleave environmental DNA in biofilms.

A promising strategy to modulate the pharmacokinetic profile of AMPs and improve their biocompatibility profile is covalent conjugation with polymers. This may be an effective approach to develop active coatings for medical implants and devices to prevent biofilm formation on their surface [70].

5.2. AMPs as Adjuvants

The use of AMPs that act on the bacterial cell wall facilitates the access of the antibiotic to its intracellular target, which allows for reducing 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 [71–76]. The antibiotic adjuvant approach 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 the 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 [4,77,78]. This creates the basis for using AMPs in new combination chemotherapeutic drugs [79]. Thus, the synergism of nisin and colistin, as well as P10 and ceftazidime/doripenem, was demonstrated against infections caused by colistin-resistant *P. aeruginosa* and extensively drug-resistant *Acinetobacter baumannii* [52].

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 [80].

Strategies and methods for de novo creating potentially active AMPs with increased antibiofilm efficacy are also discussed [81]. 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. The 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 [82]. 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 [83]. Using *Pseudomonas fluorescens* as an example, it was shown that the antimicrobial activity of the peptide nisin was increased when used synergistically with ampicillin [84].

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 [85].

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. [86], the most suitable combination was selected, which contributed to stabilizing enzymatic activity against various microorganisms (bacteria and yeast), which was higher than that of the AMPs without enzymes.

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 [87]. There is evidence of the influence of peptide length and helicity on its toxicity [62], 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 [88].

6. 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 [89].

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 [90]. 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 BAPs 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 BAPs that have a very beneficial effect on human health [91–93].

Regardless of the LAB strain, the peptides obtained with their help primarily have antimicrobial activity manifested through various mechanisms [94]. They regulate intestinal microbiota, directly inhibiting pathogenic microorganisms and promoting the growth of beneficial bacteria. The 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.

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 fugistatic [95]. 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 [96–99], affecting both the membranes of fungal cells [100], and, like antibiotics, on intracellular targets [101].

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 the 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 [102]. 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 [103]. 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 [104].

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 [105], 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* [106], 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.

Two anionic peptides (Ile-Asp-Ala-Leu-Asn-Glu-Asn-Lys and Thr-Pro-Glu-Val-Asp-Asp-Glu-Ala-Leu-Glu-Lys) exhibited antimicrobial activity against the proliferation of *Listeria* and *Staphylococcus*. It should be emphasized that AMPs are effective against a wide range of microbial hosts including Gram-negative and Gram-positive bacteria, fungi, viruses and parasites. Thus, they are not only potential natural biopreservatives but also effective in combating the rapidly increasing incidence of multidrug-resistant infections [30].

7. Production of Bioactive Peptides

Peptides for commercial purposes can be produced by liquid-phase or solid-phase synthesis, a hybrid of both solid-phase and solution-phase synthesis, or recombinant DNA technologies [107]. When obtained from foods, peptides must be released from the parent protein to be activated. This can be achieved by hydrolysis and the processing of foods by curing, fermentation, or ripening, or by digestive enzymes, including commercial proteolytic enzymes [108–110].

Plant and animal proteins are mainly used to obtain BAPs [111]. Conventional methods of BAPs receiving are fermentation, chemical and enzymatic hydrolysis. The most effective methods for the biotechnological production of peptides are enzymatic hydrolysis and the microbial fermentation of proteins [19].

7.1. Enzymatic Hydrolysis

Enzymatic hydrolysis is based on the use of commercial enzymes responsible for the cleavage of peptide bonds in proteins. This method may provide advantages in obtaining BAPs that are not provided by other methods such as fermentation, chemical hydrolysis or digestion. Among them is an improvement in the reaction rate by about 106–1012 times compared to without catalysis [112]. However, the cost of enzymes is quite high, and

there is a need for special maintenance of their activity. The yield and productivity of the process are usually low, and the formation of undesirable secondary metabolites is also possible [113]. Greater selectivity and process speed can be achieved by using ultrafiltration membranes. The method involves continuous pumping of the enzyme and substrate mixture from the reaction vessel into a membrane filter, where only small and hydrolyzed fractions pass, while large particles (polypeptides, non-hydrolyzed substrate, enzyme) are returned back to the hydrolysis tank [114]. The hydrolysis process can also be improved by pre-treating the parent protein, which ensures higher hydrolysis rates while minimizing the amount of enzyme used. Microwaves, ultrasound, high-voltage pulsed electric field, and high-pressure hydrostatic enzymatic hydrolysis are used for this purpose [114,115].

Proteolytic enzymes (proteases and peptidases) used to obtain peptides degrade proteins by hydrolyzing peptide bonds and belong to the group of hydrolases [112,116]. 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 metaloproteases [112,117,118]. 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*) [112] (Figure 1).

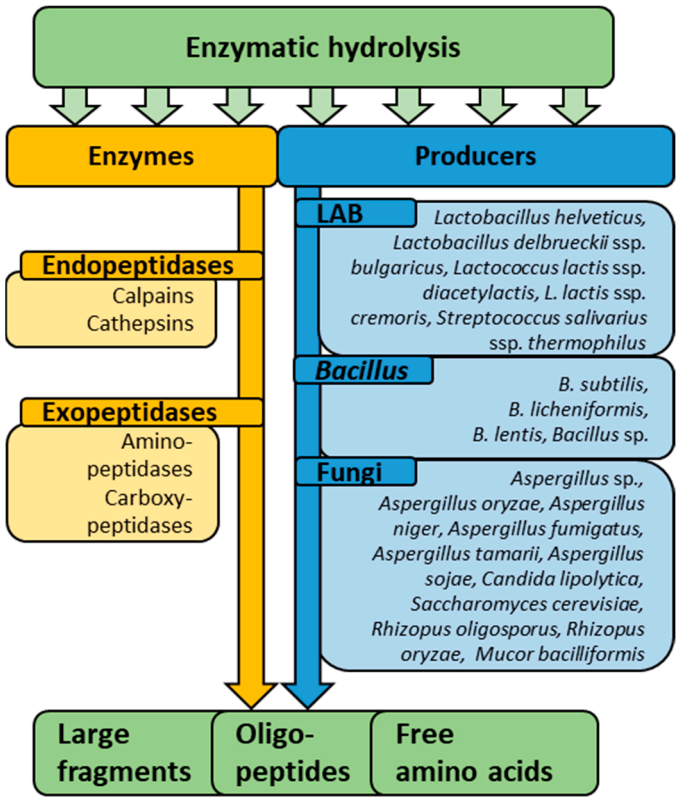

Figure 1. Receiving of bioactive peptides with enzymatic hydrolysis.

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. 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 [119]. Acid proteases (pH 2–6) produced by microorganisms are applied in the food industry for degrading milk and whey proteins, wheat gluten, and fruit juice proteins.

7.2. Novel Pre-Treatment Technologies for Enzymatic Hydrolysis

Some novel technologies are applied currently in combination with enzymatic hydrolysis. These are such eco-friendly, innovative and sustainable technologies like hydrostatic pressure processing, ultrasound-assisted and microwave-assisted extraction, pulsed electric field processing, ohmic heating, and subcritical water hydrolysis [120] (Figure 2). Figure 2 shows the technologies and enzymes used for post-treatment depending on the substrate used.

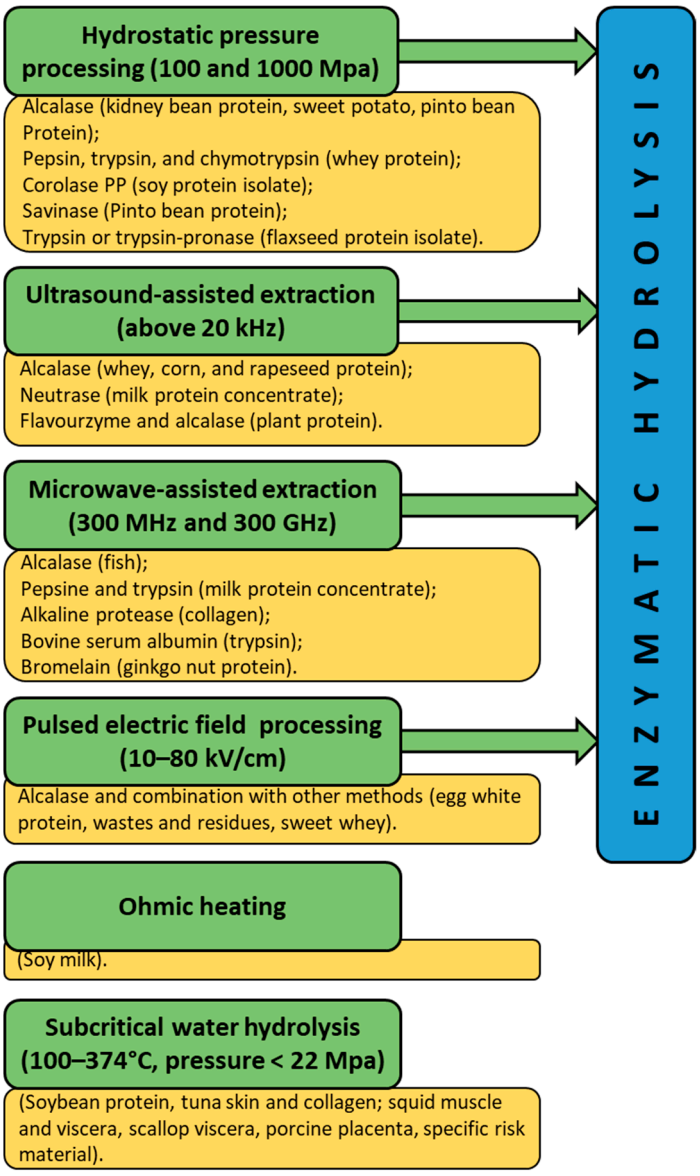

Figure 2. Novel technologies in BAPs receiving.

These technologies are mostly unable to break peptide bonds, but they promote protein denaturation and improve the accessibility of cleavage sites of enzymes, so they are used as pre-treatment before enzymatic hydrolysis. Pulsed electric field processing can break covalent bonds with repeated use, and ohmic heating is used in combination with other technologies. Subcritical water hydrolysis is the single technology that allows breaking covalent bonds, but the process is not specific and difficult to control.

7.3. Microbial Fermentation

Microbial fermentation can generate peptides of different sizes and sequences with different biological activities, as occurs during gastrointestinal digestion [121]. This 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 3) depending on the available free water volume [122].

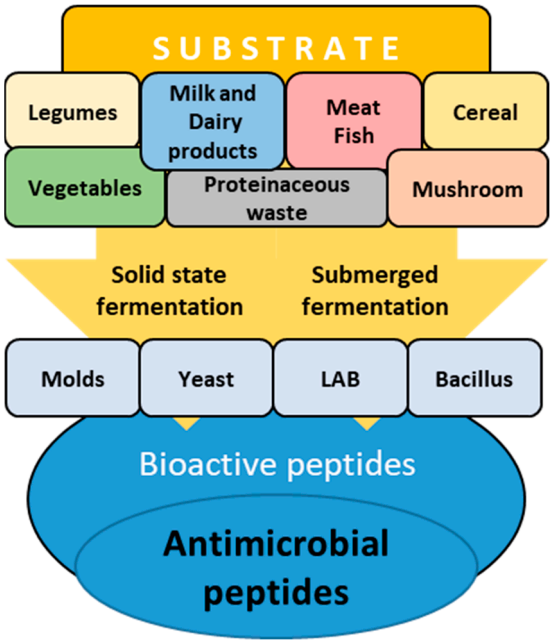

Figure 3. Receiving of bioactive peptides with microbial fermentation.

Peptidase-producing microorganisms such as filamentous fungi, yeasts, *Bacillus* species, and LAB are used to obtain BAPs [123]. To achieve the optimal production of peptides and their high bioactivity during microbial fermentation, the type of microorganism used is of crucial importance [124]. Lactic acid bacteria (LAB) are recognized as one of the most valuable microorganisms for the production of BAP due to their high adaptability to various environments, as well as to animal and plant substrates; their safety (GRAS); and most importantly, the presence of an effective and diverse proteolytic system [125,126]. The ability of microorganisms to produce extracellular and cell surface peptidases [127] 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 remain and accumulate 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*) [128]. The secondary structure of the cell-envelope proteases of LAB suggests the presence of several domains that perform different functions:

the N-terminal preprodome for secretion and activation, the catalytic serine protease domain, the 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 [129,130]. However, different types of proteases do not necessarily include all of the listed domains.

Such species of LAB as *L. bulgaricus* and *L. helveticus* have a fairly powerful proteolytic system with a wide range of proteolytic enzymes [131]. 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 the LAB inhabiting them are the best candidates for obtaining biologically active peptides.

Some yeast organisms, which also possess a set of proteases and peptidases responsible for protein degradation and belong to the GRAS category, are also widely used in dairy products to break down milk proteins and enrich them with BAP and amino acids necessary for growth [132]. Some yeasts have even better proteolytic activity than LAB. For example, according to Klein et al. (2002) [133], yeast was found to be more effective in breaking down β-casein compared to *L. helveticus.*

The microbial fermentation process can be divided into several systems. The most widely used are submerged fermentation (microorganism culture in a liquid medium containing nutrients) and solid-state fermentation (microorganism growth on nutrient-rich solid substrates). By optimizing the ratio of the microorganism used with the environmental conditions (pH, temperature, and humidity), it is possible to obtain peptides with higher bioactivity [124,126].

BAPs released during microbial fermentation are considered safer and more beneficial, without side effects, since they are obtained from edible food proteins and using safe microorganisms [134]. This makes microbial fermentation one of the preferred methods in the food industry [135].

8. 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 [136]. 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, and a significant portion of casein) as well as lactose, vitamins, minerals, and fat [137,138]. 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 [138–140]. 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, and anticancer agent [141]. Of particular value are the peptides encrypted within whey proteins, which provide the antimicrobial properties of fermented whey due to the breakdown of proteins. Bioactive whey peptides can also be obtained by enzymatic hydrolysis using digestive or microbial enzymes [142]. For example, AMPs such as isracidin and cappacin were obtained by the enzymatic hydrolysis of αS1-casein and kappa-casein, while the fermentation of αS2-casein resulted in AMPs active against *Listeria innocua*, *E. coli*, *Enterobacter sakazakii*, and *Streptococcus mutans* [19].

Currently, whey is used in 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 [143,144].

Due to its composition, including a high water content, whey is the most promising raw material in the beverage industry [145–148], including the addition of other components that improve their biological and nutritional characteristics [149–151]. It is also promising for the production of biologically active substances, including AMPs [152,153], both in the form of pure preparations and in the form of drinks fortified with them [154–164].

Returning whey to the food chain in a palatable form is a hot topic in the literature [143,165]. 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 [166].

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 [148]. 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 [167]. 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 [168–171], including those known to be antibiotic-resistant. Most attention has been paid to AMPs exhibiting antibiofilm activity [172–176], since biofilm formation is a major factor contributing to antibiotic tolerance with increased infection severity, incidence, treatment failure, and mortality [177]. 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 they have also been successfully used to treat some ulcers and some types of cancer [178].

The staff of the food microbiology laboratory of the Research and Production Center of Microbiology and Virology (Almaty, Kazakhstan) has 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 [179–182]. As a result of the studies, functional whey-based beverages [183,184] were proposed that actively affect the indigenous microbiota [185] and are promising for use as probiotic products [186,187]. Whey-based drinks, due to the content of probiotic microorganisms [149–151,156] 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.

9. 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 [188]. 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 [189]. Marine actinobacteria are recognized as promising for the development as sources of new antibiotics and biofilm inhibitor molecules [190].

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 [191].

To address the problem of combating infections, the 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 BAPs [109]. 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 [192]. For example, unnatural amino acids can be used to create artificial AMPs with improved properties, and this can guide future antimicrobial drug design considerations [193]. It is envisaged that synthetic AMP analogs designed with some modifications can overcome the stability, toxicity, and activity limitations of naturally occurring AMPs [194]. Thus, Zhang et al. [195] developed a series of short mirror-symmetric peptides, among which LWWRRRWWL-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 [11]. To overcome these limitations, peptide engineering techniques and the development of cost-effective algorithms for predicting AMPs with minimal toxicity [196] have been used, and some of them have now reached the commercialization stage in several pharmaceutical industries [197].

The 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 are 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 the 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 [198].

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 [199]. Computer modeling (in silico) can be a useful tool for the 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 [200]. 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 [201].

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 [202]. However, before they can fully replace antimicrobials in food production, difficulties associated with standardization and manufacturing on a commercial scale need to be overcome [203].

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 and Hammami [204], 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 [205–207]. Microbial metabolites such as biosurfactants, AMPs, enzymes, and bioactive compounds have been identified as promising broad-spectrum antibiofilm agents [208] with peptides being evaluated as the most potent antibiofilm agents [209]. Thus,

the peptide-based approach becomes a promising alternative for effectively combating the notorious resistant biofilms.

10. 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 [197]. 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 [210]. 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.

Author Contributions: Writing—original draft preparation and project administration, M.S.; writing—review and editing, Y.O., A.R. and Z.Y.; formal analysis, A.R.; resources, Z.Y.; validation and data curation, Y.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP19674760).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Vaňková, E.; Julák, J.; Machková, A.; Obrová, K.; Klančnik, A.; Smole Možina, S.; Scholtz, V. Overcoming antibiotic resistance: Non-thermal plasma and antibiotics combination inhibits important pathogens. *Pathog. Dis.* **2024**, *82*, ftae007. [CrossRef] [PubMed]
2. Adefisoye, M.A.; Olaniran, A.O. Antimicrobial resistance expansion in pathogens: A review of current mitigation strategies and advances towards innovative therapy. *JAC-AMR* **2023**, *5*, dlad127. [CrossRef]
3. Frieden, T. *Antibiotic Resistance Threats in the United States*; Centers for Disease Control and Prevention (CDC): Atlanta, GA, USA, 2019.
4. Lewies, A.; Du Plessis, L.H.; Wentzel, J.F. Antimicrobial peptides: The Achilles' heel of antibiotic resistance? *Probiotics Antimicrob. Proteins* **2019**, *11*, 370–381. [CrossRef]
5. Ioannou, P.; Baliou, S.; Kofteridis, D.P. Antimicrobial peptides in infectious diseases and beyond—A narrative review. *Life* **2023**, *13*, 1651. [CrossRef]
6. Chakraborty, S.; Chatterjee, R.; Chakravortty, D. Evolving and assembling to pierce through: Evolutionary and structural aspects of antimicrobial peptides. *Comput. Struct. Biotechnol. J.* **2022**, *20*, 2247–2258. [CrossRef]

7. Mihaylova-Garnizova, R.; Davidova, S.; Hodzhev, Y.; Satchanska, G. Antimicrobial Peptides Derived from Bacteria: Classification, Sources, and Mechanism of Action against Multidrug-Resistant Bacteria. *Int. J. Mol. Sci.* **2024**, *25*, 10788. [CrossRef]
8. Andrea, A.; Molchanova, N.; Jenssen, H. Antibiofilm peptides and peptidomimetics with focus on surface immobilization. *Biomolecules* **2018**, *8*, 27. [CrossRef]
9. Haney, E.F.; Straus, S.K.; Hancock, R.E. Reassessing the host defense peptide landscape. *Front. Chem.* **2019**, *7*, 435645. [CrossRef]
10. Raheem, N.; Straus, S.K. Mechanisms of action for antimicrobial peptides with antibacterial and antibiofilm functions. *Front. Microbiol.* **2019**, *10*, 2866. [CrossRef]
11. Mahlapuu, M.; Björn, C.; Ekblom, J. Antimicrobial peptides as therapeutic agents: Opportunities and challenges. *Crit. Rev. Biotechnol.* **2020**, *40*, 978–992. [CrossRef]
12. Mookherjee, N.; Anderson, M.A.; Haagsman, H.P.; Davidson, D.J. Antimicrobial host defence peptides: Functions and clinical potential. *Nat. Rev. Drug Discov.* **2020**, *19*, 311–332. [CrossRef]
13. Talapko, J.; Meštrović, T.; Juzbašić, M.; Tomas, M.; Erić, S.; Horvat Aleksijević, L.; Bekić, S.; Schwarz, D.; Matić, S.; Neuberg, M.; et al. Antimicrobial peptides—Mechanisms of action, antimicrobial effects and clinical applications. *Antibiotics* **2022**, *11*, 1417. [CrossRef]
14. Bucataru, C.; Ciobanasu, C. Antimicrobial peptides: Opportunities and challenges in overcoming resistance. *Microbiol Res.* **2024**, *286*, 127822. [CrossRef]
15. Singh, G.; Rana, A.; Smriti. Decoding antimicrobial resistance: Unraveling molecular mechanisms and targeted strategies. *Arch. Microbiol.* **2024**, *206*, 280. [CrossRef]
16. Seyfi, R.; Kahaki, F.A.; Ebrahimi, T.; Montazersaheb, S.; Eyvazi, S.; Babaeipour, V.; Tarhriz, V. Antimicrobial peptides (AMPs): Roles, functions and mechanism of action. *Int. J. Pept. Res. Ther.* **2020**, *26*, 1451–1463. [CrossRef]
17. Lazzaro, B.P.; Zasloff, M.; Rolff, J. Antimicrobial peptides: Application informed by evolution. *Science* **2020**, *368*, eaau5480. [CrossRef]
18. Yan, Y.; Li, Y.; Zhang, Z.; Wang, X.; Niu, Y.; Zhang, S.; Xu, W.; Ren, C. Advances of peptides for antibacterial applications. *Colloids Surf. B Biointerfaces* **2021**, *202*, 111682. [CrossRef]
19. Saubenova, M.; Oleinikova, Y.; Rapoport, A.; Maksimovich, S.; Yermekbay, Z.; Khamedova, E. Bioactive Peptides Derived from Whey Proteins for Health and Functional Beverages. *Fermentation* **2024**, *10*, 359. [CrossRef]
20. Hancock, R.E.; Haney, E.F.; Gill, E.E. The immunology of host defence peptides: Beyond antimicrobial activity. *Nat. Rev. Immunol.* **2016**, *16*, 321–334. [CrossRef]
21. Kormilets, D.Y.; Polyanovsky, A.D.; Dadalic, V.A.; Maryanovich, A.T. Antibiotic Peptides. *Zhurnal Jevoljucionnoj Biohim. I Fiziol.* **2019**, *55*, 242–248. (In Russian) [CrossRef]
22. Hassan, M.; Flanagan, T.W.; Kharouf, N.; Bertsch, C.; Mancino, D.; Haikel, Y. Antimicrobial proteins: Structure, molecular action, and therapeutic potential. *Pharmaceutics* **2022**, *15*, 72. [CrossRef] [PubMed]
23. Zhao, Q.; He, L.; Wang, X.; Ding, X.; Li, L.; Tian, Y.; Huang, A. Characterization of a novel antimicrobial peptide isolated from Moringa oleifera seed protein hydrolysates and its membrane damaging effects on Staphylococcus aureus. *J. Agric. Food Chem.* **2022**, *70*, 6123–6133. [CrossRef] [PubMed]
24. Mulkern, A.J.; Oyama, L.B.; Cookson, A.R.; Creevey, C.J.; Wilkinson, T.J.; Olleik, H.; da Silva, G.C.; Fontes, P.P.; Bazzolli, D.M.S.; Mantovani, H.C.; et al. Microbiome-derived antimicrobial peptides offer therapeutic solutions for the treatment of Pseudomonas aeruginosa infections. *Npj Biofilms Microbiomes* **2022**, *8*, 70. [CrossRef] [PubMed]
25. Huan, Y.; Kong, Q.; Mou, H.; Yi, H. Antimicrobial peptides: Classification, design, application and research progress in multiple fields. *Front. Microbiol.* **2020**, *11*, 582779. [CrossRef]
26. Vilas Boas, L.C.P.; Campos, M.L.; Berlanda, R.L.A.; de Carvalho Neves, N.; Franco, O.L. Antiviral peptides as promising therapeutic drugs. *Cell. Mol. Life Sci.* **2019**, *76*, 3525–3542. [CrossRef]
27. Ashaolu, T.J.; Nawaz, A.; Walayat, N.; Khalifa, I. Potential "biopeptidal" therapeutics for severe respiratory syndrome coronaviruses: A review of antiviral peptides, viral mechanisms, and prospective needs. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 3457–3470. [CrossRef]
28. LeeYing-Chiang, J.; ShirkeyJaden, D.; CowanAlexis, J. An overview of antiviral peptides and rational biodesign considerations. *BioDesign Res.* **2022**, *2022*, 9898241. [CrossRef]
29. Jan, Z.; Geethakumari, A.M.; Biswas, K.H.; Jithesh, P.V. Protegrin-2, a potential inhibitor for targeting SARS-CoV-2 main protease Mpro. *Comput. Struct. Biotechnol. J.* **2023**, *21*, 3665–3671. [CrossRef]
30. Danquah, M.K.; Agyei, D. Pharmaceutical applications of bioactive peptides. *OA Biotechnol.* **2012**, *1*, 1–7. [CrossRef]
31. de la Fuente-Núñez, C.; Silva, O.N.; Lu, T.K.; Franco, O.L. Antimicrobial peptides: Role in human disease and potential as immunotherapies. *Pharmacol. Therap.* **2017**, *178*, 132–140. [CrossRef]
32. Răileanu, M.; Borlan, R.; Campu, A.; Janosi, L.; Turcu, I.; Focsan, M.; Bacalum, M. No country for old antibiotics! Antimicrobial peptides (AMPs) as next-generation treatment for skin and soft tissue infection. *Int. J. Pharm.* **2023**, *642*, 123169. [CrossRef] [PubMed]

33. Gera, S.; Kankuri, E.; Kogermann, K. Antimicrobial peptides–unleashing their therapeutic potential using nanotechnology. *Pharmacol. Ther.* **2022**, *232*, 107990. [CrossRef] [PubMed]
34. Li, J.; Hu, S.; Jian, W.; Xie, C.; Yang, X. Plant antimicrobial peptides: Structures, functions, and applications. *Bot. Stud.* **2021**, *62*, 5. [CrossRef]
35. Li, S.; Wang, Y.; Xue, Z.; Jia, Y.; Li, R.; He, C.; Chen, H. The structure-mechanism relationship and mode of actions of antimicrobial peptides: A review. *Trends Food Sci.* **2021**, *109*, 103–115. [CrossRef]
36. Zhang, Q.Y.; Yan, Z.B.; Meng, Y.M.; Hong, X.Y.; Shao, G.; Ma, J.J.; Cheng, X.R.; Liu, J.; Kang, J.; Fu, C.Y. Antimicrobial peptides: Mechanism of action, activity and clinical potential. *Mil. Med. Res.* **2021**, *8*, 48. [CrossRef]
37. Powers, J.P.; Hancock, R.E. The relationship between peptide structure and antibacterial activity. *Peptides* **2003**, *24*, 1681–1691. [CrossRef]
38. Boehr, D.D.; Draker, K.A.; Koteva, K.; Bains, M.; Hancock, R.E.; Wright, G.D. Broad-spectrum peptide inhibitors of aminoglycoside antibiotic resistance enzymes. *Chem. Biol.* **2003**, *10*, 189–196. [CrossRef]
39. Steckbeck, J.D.; Deslouches, B.; Montelaro, R.C. Antimicrobial peptides: New drugs for bad bugs? *Expert Opin Biol. Ther.* **2014**, *14*, 11–14. [CrossRef]
40. Koczulla, R.; Von Degenfeld, G.; Kupatt, C.; Krötz, F.; Zahler, S.; Gloe, T.; Issbrücker, K.; Unterberger, P.; Zaiou, M.; Lebherz, C.; et al. An angiogenic role for the human peptide antibiotic LL-37/hCAP-18. *J. Clin. Investig.* **2003**, *111*, 1665–1672. [CrossRef]
41. Khavinson, V.K.; Popovich, I.G.E.; Linkova, N.S.; Mironova, E.S.; Ilina, A.R. Peptide regulation of gene expression: A systematic review. *Molecules* **2021**, *26*, 7053. [CrossRef]
42. Gagat, P.; Ostrówka, M.; Duda-Madej, A.; Mackiewicz, P. Enhancing antimicrobial peptide activity through modifications of charge, hydrophobicity, and structure. *Int. J. Mol. Sci.* **2024**, *25*, 10821. [CrossRef]
43. Goki, N.H.; Tehranizadeh, Z.A.; Saberi, M.R.; Khameneh, B.; Bazzaz, B.S. Structure, function, and physicochemical properties of pore-forming antimicrobial peptides. *Curr. Pharm. Biotechnol.* **2024**, *25*, 1041–1057. [CrossRef] [PubMed]
44. Rossino, G.; Marchese, E.; Galli, G.; Verde, F.; Finizio, M.; Serra, M.; Linciano, P.; Collina, S. Peptides as therapeutic agents: Challenges and opportunities in the green transition era. *Molecules* **2023**, *28*, 7165. [CrossRef] [PubMed]
45. Browne, K.; Chakraborty, S.; Chen, R.; Willcox, M.D.; Black, D.S.; Walsh, W.R.; Kumar, N. A new era of antibiotics: The clinical potential of antimicrobial peptides. *Int. J. Mol. Sci.* **2020**, *21*, 7047. [CrossRef] [PubMed]
46. Bolatchiev, A. Antimicrobial Peptides Epinecidin-1 and Beta-Defesin-3 Are Effective against a Broad Spectrum of Antibiotic-Resistant Bacterial Isolates and Increase Survival Rate in Experimental Sepsis. *Antibiotics* **2022**, *11*, 76. [CrossRef] [PubMed]
47. Huang, Y.; Yang, N.; Teng, D.; Mao, R.; Hao, Y.; Ma, X.; Wei, l.; Wang, J. Antibacterial peptide NZ2114-loaded hydrogel accelerates Staphylococcus aureus-infected wound healing. *Appl. Microbiol. Biotechnol.* **2022**, *106*, 3639–3656. [CrossRef]
48. Yuan, Z.; Tam, V.H. Polymyxin B: A new strategy for multidrug-resistant Gram-negative organisms. *Expert Opin. Investig. Drugs.* **2008**, *17*, 661–668. [CrossRef]
49. Zavascki, A.P.; Goldani, L.Z.; Li, J.; Nation, R.L. Polymyxin B for the treatment of multidrug-resistant pathogens: A critical review. *J. Antimicrob. Chemother.* **2007**, *60*, 1206–1215. [CrossRef]
50. Gallardo-Godoy, A.; Muldoon, C.; Becker, B.; Elliott, A.G.; Lash, L.H.; Huang, J.X.; Butler, M.S.; Pelingon, R.; Kavanagh, A.M.; Ramu, S.; et al. Activity and predicted nephrotoxicity of synthetic antibiotics based on polymyxin B. *J. Med. Chem.* **2016**, *59*, 1068–1077. [CrossRef]
51. Severino, P.; Silveira, E.F.; Loureiro, K.; Chaud, M.V.; Antonini, D.; Lancellotti, M.; Sarmento, V.H.; da Silva, C.F.; Santana, M.H.A.; Souto, E.B. Antimicrobial activity of polymyxin-loaded solid lipid nanoparticles (PLX-SLN): Characterization of physicochemical properties and in vitro efficacy. *Eur. J. Pharm. Sci.* **2017**, *106*, 177–184. [CrossRef]
52. Jahangiri, A.; Neshani, A.; Mirhosseini, S.A.; Ghazvini, K.; Zare, H.; Sedighian, H. Synergistic effect of two antimicrobial peptides, Nisin and P10 with conventional antibiotics against extensively drug-resistant Acinetobacter baumannii and colistin-resistant *Pseudomonas aeruginosa* isolates. *Microb. Pathog.* **2021**, *150*, 104700. [CrossRef] [PubMed]
53. Musin, H.G. Antimicrobial peptides are a potential replacement for traditional antibiotics. *Infect. Immun.* **2018**, *8*, 295–308. [CrossRef]
54. Bian, X.; Qu, X.; Zhang, J.; Nang, S.C.; Bergen, P.J.; Zhou, Q.T.; Chan, H.K.; Feng, M.; Li, J. Pharmacokinetics and pharmacodynamics of peptide antibiotics. *Adv. Drug Deliv. Rev.* **2022**, *183*, 114171. [CrossRef] [PubMed]
55. Deva, A.K.; Adams Jr, W.P.; Vickery, K. The role of bacterial biofilms in device-associated infection. *Plast. Reconstr. Surg.* **2013**, *132*, 1319–1328. [CrossRef]
56. Chung, P.Y.; Khanum, R. Antimicrobial peptides as potential anti-biofilm agents against multidrug-resistant bacteria. *J. Microbiol. Immunol. Infect.* **2017**, *50*, 405–410. [CrossRef]
57. Lopes, B.S.; Hanafiah, A.; Nachimuthu, R.; Muthupandian, S.; Md Nesran, Z.N.; Patil, S. The role of antimicrobial peptides as antimicrobial and antibiofilm agents in tackling the silent pandemic of antimicrobial resistance. *Molecules* **2022**, *27*, 2995. [CrossRef]

58. Cavallo, I.; Sivori, F.; Mastrofrancesco, A.; Abril, E.; Pontone, M.; Di Domenico, E.G.; Pimpinelli, F. Bacterial biofilm in chronic wounds and possible therapeutic approaches. *Biology* **2024**, *13*, 109. [CrossRef]
59. Yasir, M.; Willcox, M.D.P.; Dutta, D. Action of antimicrobial peptides against bacterial biofilms. *Materials* **2018**, *11*, 2468. [CrossRef]
60. Nag, M.; Bhattacharya, D.; Garai, S.; Dutta, B.; Ghosh, S.; Ray, R.R.; Lahiri, D. Immobilised antimicrobial peptides in downregulation of biofilm. *Naunyn Schmiedebergs Arch. Pharmacol.* **2024**, *397*, 5559–5569. [CrossRef]
61. Surekha, S.; Lamiyan, A.K.; Gupta, V. Antibiotic resistant biofilms and the quest for novel therapeutic strategies. *Indian J. Microbiol.* **2024**, *64*, 20–35. [CrossRef]
62. Bahar, A.A.; Ren, D. Antimicrobial peptides. *Pharmaceuticals* **2013**, *6*, 1543–1575. [CrossRef] [PubMed]
63. Di Somma, A.; Moretta, A.; Canè, C.; Cirillo, A.; Duilio, A. Antimicrobial and antibiofilm peptides. *Biomolecules* **2020**, *10*, 652. [CrossRef] [PubMed]
64. Pletzer, D.; Coleman, S.R.; Hancock, R.E. Anti-biofilm peptides as a new weapon in antimicrobial warfare. *Curr. Opin Microbiol.* **2016**, *33*, 35–40. [CrossRef]
65. Dawgul, M.; Maciejewska, M.; Jaskiewicz, M.; Karafova, A.; Kamysz, W. Antimicrobial peptides as potential tool to fight bacterial biofilm. *Acta Pol. Pharm.* **2014**, *71*, 39–47.
66. Batoni, G.; Maisetta, G.; Esin, S. Antimicrobial peptides and their interaction with biofilms of medically relevant bacteria. *BBA-Biomembr.* **2016**, *1858*, 1044–1060. [CrossRef]
67. Malanovic, N.; Lohner, K. Gram-positive bacterial cell envelopes: The impact on the activity of antimicrobial peptides. *BBA-Biomembr.* **2016**, *1858*, 936–946. [CrossRef]
68. Segev-Zarko, L.A.; Shai, Y. Methods for investigating biofilm inhibition and degradation by antimicrobial peptides. In *Antimicrobial Peptides: Methods and Protocols*; Humana Press: New York, NY, USA, 2017; pp. 309–322. [CrossRef]
69. Portelinha, J.; Angeles-Boza, A.M. The antimicrobial peptide Gad-1 clears Pseudomonas aeruginosa biofilms under cystic fibrosis conditions. *ChemBioChem* **2021**, *22*, 1646–1655. [CrossRef]
70. Bellotto, O.; Semeraro, S.; Bandiera, A.; Tramer, F.; Pavan, N.; Marchesan, S. Polymer Conjugates of Antimicrobial Peptides (AMPs) with D-Amino Acids (D-aa): State of the Art and Future Opportunities. *Pharmaceutics* **2022**, *14*, 446. [CrossRef]
71. Doern, C.D. When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. *J. Clin. Microbiol.* **2014**, *52*, 4124–4128. [CrossRef]
72. Wu, X.; Li, Z.; Li, X.; Tian, Y.; Fan, Y.; Yu, C.; Zhou, B.; Liu, Y.; Xiang, R.; Yang, L. Synergistic effects of antimicrobial peptide DP7 combined with antibiotics against multidrug-resistant bacteria. *Drug Des. Dev. Ther.* **2017**, *11*, 939–946. [CrossRef]
73. Kampshoff, F.; Willcox, M.D.; Dutta, D. A pilot study of the synergy between two antimicrobial peptides and two common antibiotics. *Antibiotics* **2019**, *8*, 60. [CrossRef] [PubMed]
74. Pizzolato-Cezar, L.R.; Okuda-Shinagawa, N.M.; Machini, M.T. Combinatory therapy antimicrobial peptide-antibiotic to minimize the ongoing rise of resistance. *Front. Microbiol.* **2019**, *10*, 1703. [CrossRef]
75. Ruden, S.; Rieder, A.; Chis Ster, I.; Schwartz, T.; Mikut, R.; Hilpert, K. Synergy pattern of short cationic antimicrobial peptides against multidrug-resistant *Pseudomonas aeruginosa*. *Front. Microbiol.* **2019**, *10*, 2740. [CrossRef]
76. Chen, C.; Shi, J.; Wang, D.; Kong, P.; Wang, Z.; Liu, Y. Antimicrobial peptides as promising antibiotic adjuvants to combat drug-resistant pathogens. *Crit. Rev. Microbiol.* **2024**, *50*, 267–284. [CrossRef]
77. Hollmann, A.; Martinez, M.; Maturana, P.; Semorile, L.C.; Maffia, P.C. Antimicrobial peptides: Interaction with model and biological membranes and synergism with chemical antibiotics. *Front. Chem.* **2018**, *6*, 204. [CrossRef]
78. Zhu, Y.; Hao, W.; Wang, X.; Ouyang, J.; Deng, X.; Yu, H.; Wang, Y. Antimicrobial peptides, conventional antibiotics, and their synergistic utility for the treatment of drug-resistant infections. *Med. Res. Rev.* **2022**, *42*, 1377–1422. [CrossRef]
79. Li, J.; Fernández-Millán, P.; Boix, E. Synergism between host defence peptides and antibiotics against bacterial infections. *Curr. Top Med. Chem.* **2020**, *20*, 1238–1263. [CrossRef]
80. Hadjicharalambous, A.; Bournakas, N.; Newman, H.; Skynner, M.J.; Beswick, P. Antimicrobial and cell-penetrating peptides: Understanding penetration for the design of novel conjugate antibiotics. *Antibiotics* **2022**, *11*, 1636. [CrossRef]
81. Di Luca, M.; Maccari, G.; Nifosì, R. Treatment of microbial biofilms in the post-antibiotic era: Prophylactic and therapeutic use of antimicrobial peptides and their design by bioinformatics tools. *Pathog. Dis.* **2014**, *70*, 257–270. [CrossRef]
82. Segev-Zarko, L.A.; Saar-Dover, R.; Brumfeld, V.; Mangoni, M.L.; Shai, Y. Mechanisms of biofilm inhibition and degradation by antimicrobial peptides. *Biochem. J.* **2015**, *468*, 259–270. [CrossRef]
83. Chen, X.; Su, S.; Yan, Y.; Yin, L.; Liu, L. Anti-*Pseudomonas aeruginosa* activity of natural antimicrobial peptides when used alone or in combination with antibiotics. *Front. Microbiol.* **2023**, *14*, 1239540. [CrossRef] [PubMed]
84. Biswaro, L.S.; da Costa Sousa, M.G.; Rezende, T.M.; Dias, S.C.; Franco, O.L. Antimicrobial peptides and nanotechnology, recent advances and challenges. *Front. Microbiol.* **2018**, *9*, 855. [CrossRef] [PubMed]
85. Wei, D.; Zhang, X. Biosynthesis, bioactivity, biotoxicity and applications of antimicrobial peptides for human health. *Biosaf. Health* **2022**, *4*, 118–134. [CrossRef]

86. Aslanli, A.; Domnin, M.; Stepanov, N.; Senko, O.; Efremenko, E. Action enhancement of antimicrobial peptides by their combination with enzymes hydrolyzing fungal quorum molecules. *Int. J. Biol. Macromol.* **2024**, *280*, 136066. [CrossRef] [PubMed]
87. Enninful, G.N.; Kuppusamy, R.; Tiburu, E.K.; Kumar, N.; Willcox, M.D. Non-canonical amino acid bioincorporation into antimicrobial peptides and its challenges. *J. Pept. Sci.* **2024**, *30*, e3560. [CrossRef]
88. Xuan, J.; Feng, W.; Wang, J.; Wang, R.; Zhang, B.; Bo, L.; Chen, Z.S.; Yang, H.; Sun, L. Antimicrobial peptides for combating drug-resistant bacterial infections. *Drug Resist Updat.* **2023**, *68*, 100954. [CrossRef]
89. Kamel, M.; Aleya, S.; Alsubih, M.; Aleya, L. Microbiome Dynamics: A Paradigm Shift in Combatting Infectious Diseases. *J. Pers. Med.* **2024**, *14*, 217. [CrossRef]
90. Baindara, P.; Mandal, S.M. Gut-antimicrobial peptides: Synergistic co-evolution with antibiotics to combat multi-antibiotic resistance. *Antibiotics* **2023**, *12*, 1732. [CrossRef]
91. Toldrá, F.; Reig, M.; Aristoy, M.C.; Mora, L. Generation of bioactive peptides during food processing. *Food Chem.* **2018**, *267*, 395–404. [CrossRef]
92. Guzmán-Rodríguez, F.; Gómez-Ruiz, L.; Rodríguez-Serrano, G.; Alatorre-Santamaría, S.; García-Garibay, M.; Cruz-Guerrero, A. Iron binding and antithrombotic peptides released during the fermentation of milk by *Lactobacillus casei* shirota. *Rev. Mex. Ing. Química* **2019**, *18*, 1161–1165. [CrossRef]
93. Bao, X.; Wu, J. Impact of food-derived bioactive peptides on gut function and health. *Food Res. Int.* **2021**, *147*, 110485. [CrossRef] [PubMed]
94. Fernandez, M.A.; Marette, A. Novel perspectives on fermented milks and cardiometabolic health with a focus on type 2 diabetes. *Nutr. Rev.* **2018**, *76*, 16–28. [CrossRef] [PubMed]
95. Freitas, C.G.; Franco, O.L. Antifungal peptides with potential against pathogenic fungi. In *Recent Trends in Antifungal Agents and Antifungal Therapy*; Basak, A., Chakraborty, R., Mandal, S., Eds.; Springer: New Delhi, India, 2016; pp. 75–95. [CrossRef]
96. Rouse, S.; Harnett, D.; Vaughan, A.; Sinderen, D.V. Lactic acid bacteria with potential to eliminate fungal spoilage in foods. *J. Appl. Microbiol.* **2008**, *104*, 915–923. [CrossRef] [PubMed]
97. Dalié, D.K.D.; Deschamps, A.M.; Richard-Forget, F. Lactic acid bacteria–Potential for control of mould growth and mycotoxins: A review. *Food Control* **2010**, *21*, 370–380. [CrossRef]
98. Cizeikiene, D.; Juodeikiene, G.; Paskevicius, A.; Bartkiene, E. Antimicrobial activity of lactic acid bacteria against pathogenic and spoilage microorganism isolated from food and their control in wheat bread. *Food Control* **2013**, *31*, 539–545. [CrossRef]
99. Crowley, S.; Mahony, J.; van Sinderen, D. Current perspectives on antifungal lactic acid bacteria as natural bio-preservatives. *Trends Food Sci. Technol.* **2013**, *33*, 93–109. [CrossRef]
100. Rautenbach, M.; Troskie, A.M.; Vosloo, J.A. Antifungal peptides: To be or not to be membrane active. *Biochimie* **2016**, *130*, 132–145. [CrossRef]
101. Fernández de Ullivarri, M.; Arbulu, S.; Garcia-Gutierrez, E.; Cotter, P.D. Antifungal peptides as therapeutic agents. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 105. [CrossRef]
102. Kumariya, R.; Garsa, A.K.; Rajput, Y.S.; Sood, S.K.; Akhtar, N.; Patel, S. Bacteriocins: Classification, synthesis, mechanism of action and resistance development in food spoilage causing bacteria. *Microb. Pathog.* **2019**, *128*, 171–177. [CrossRef]
103. Kamal, I.; Ashfaq, U.A.; Hayat, S.; Aslam, B.; Sarfraz, M.H.; Yaseen, H.; Rajoka, M.S.R.; Shah, A.A.; Khurshid, M. Prospects of antimicrobial peptides as an alternative to chemical preservatives for food safety. *Biotechnol. Lett.* **2023**, *45*, 137–162. [CrossRef]
104. Luz, C.; Izzo, L.; Ritieni, A.; Mañes, J.; Meca, G. Antifungal and antimycotoxigenic activity of hydrolyzed goat whey on *Penicillium* spp: An application as biopreservation agent in pita bread. *LWT* **2020**, *118*, 108717. [CrossRef]
105. Singh, B.P.; Rohit; Manju, K.M.; Sharma, R.; Bhushan, B.; Ghosh, S.; Goel, G. Nano-conjugated food-derived antimicrobial peptides as natural biopreservatives: A review of technology and applications. *Antibiotics* **2023**, *12*, 244. [CrossRef] [PubMed]
106. Barbosa, A.A.T.; Mantovani, H.C.; Jain, S. Bacteriocins from lactic acid bacteria and their potential in the preservation of fruit products. *Crit. Rev. Biotechnol.* **2017**, *37*, 852–864. [CrossRef]
107. Kota, S. Peptide Manufacturing Methods and Challenges. 2019 Ebook Collection. 2019; pp. 111–150. Available online: https://books.rsc.org/books/edited-volume/801/chapter-abstract/541398/Peptide-Manufacturing-Methods-and-Challenges (accessed on 10 December 2024). [CrossRef]
108. Bersi, G.; Barberis, S.E.; Origone, A.L.; Adaro, M.O. Bioactive peptides as functional food ingredients. In *Role of Materials Science in Food Bioengineering*; Academic Press: London, UK, 2018; pp. 147–186. [CrossRef]
109. Chauhan, V.; Kanwar, S.S. Bioactive peptides: Synthesis, functions and biotechnological applications. In *Biotechnological Production of Bioactive Compounds*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 107–137.
110. Daliri, E.B.-M.; Oh, D.H.; Lee, B.H. Bioactive Peptides. *Foods* **2017**, *6*, 32. [CrossRef]
111. Cruz-Casas, D.E.; Aguilar, C.N.; Ascacio-Valdés, J.A.; Rodríguez-Herrera, R.; Chávez-González, M.L.; Flores-Gallegos, A.C. Enzymatic hydrolysis and microbial fermentation: The most favorable biotechnological methods for the release of bioactive peptides. *Food Chem. Mol. Sci.* **2021**, *3*, 100047. [CrossRef]

112. Martínez-Medina, G.A.; Barragán, A.P.; Ruiz, H.A.; Ilyina, A.; Hernández, J.L.M.; Rodríguez-Jasso, R.M.; Hoyos-Concha, J.L.; Aguilar-González, C.N. Fungal proteases and production of bioactive peptides for the food industry. In *Enzymes in Food Biotechnology*; Academic Press: London, UK, 2019; pp. 221–246. [CrossRef]
113. Cruz-Casas, D.E.; Chavez-García, S.N.; García-Flores, L.A.; Martinez-Medina, G.A.; Ramos-González, R.; Prado-Barragán, L.A.; Flores-Gallegos, A.C. Bioactive peptides from fermented milk products. In *Enzymes Beyond Traditional Applications in Dairy Science and Technology*; Academic Press: London, UK, 2023; pp. 289–311. [CrossRef]
114. Rizzello, C.G.; Cassone, A.; Coda, R.; Gobbetti, M. Antifungal activity of sourdough fermented wheat germ used as an ingredient for bread making. *Food Chem.* **2011**, *127*, 952–959. [CrossRef]
115. Sergey, M.; Nadia, B.; Eugène, V.; Laurent, B. High voltage electrical treatments to improve the protein susceptibility to enzymatic hydrolysis. *ACS Sustain. Chem. Eng.* **2017**, *5*, 11706–11714. [CrossRef]
116. Souza, T.S.P.D.; de Andrade, C.J.; Koblitz, M.G.B.; Fai, A.E.C. Microbial peptidase in food processing: Current state of the art and future trends. *Catal. Lett.* **2023**, *153*, 114–137. [CrossRef]
117. Rao, M.B.; Tanksale, A.M.; Ghatge, M.S.; Deshpande, V.V. Molecular and biotechnological aspects of microbial proteases. *Microbiol. Mol. Biol.* **1998**, *62*, 597–635. [CrossRef]
118. Whitaker, J.R. *Principles of Enzymology for the Food Science*, 2nd ed.; Routledge: New York, NY, USA, 2018; 648p. [CrossRef]
119. Song, P.; Zhang, X.; Wang, S.; Xu, W.; Wang, F.; Fu, R.; Wei, F. Microbial proteases and their applications. *Front. Microbiol.* **2023**, *14*, 1236368. [CrossRef]
120. Ulug, S.K.; Jahandideh, F.; Wu, J. Novel technologies for the production of bioactive peptides. *Trends Food Sci.* **2021**, *108*, 27–39. [CrossRef]
121. Park, Y.W.; Nam, M.S. Bioactive peptides in milk and dairy products: A review. *Korean J. Food Sci. Anim. Resour.* **2015**, *35*, 831–840. [CrossRef] [PubMed]
122. Chai, K.F.; Voo, A.Y.H.; Chen, W.N. Bioactive peptides from food fermentation: A comprehensive review of their sources, bioactivities, applications, and future development. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 3825–3885. [CrossRef]
123. Kumari, R.; Sanjukta, S.; Sahoo, D.; Rai, A.K. Functional peptides in Asian protein rich fermented foods: Production and health benefits. *Syst. Microbiol. Biomanufacturing* **2022**, *2*, 1–13. [CrossRef]
124. Hayes, M.; García-Vaquero, M. Bioactive compounds from fermented food products. In *Novel Food Fermentation Technologies*; Springer: Cham, Switzerland, 2016; pp. 293–310. [CrossRef]
125. Lafarga, T.; Hayes, M. Effect of pre-treatment on the generation of dipeptidyl peptidase-IV-and prolyl endopeptidase-inhibitory hydrolysates from bovine lung. *Ir. J. Agric. Food Res.* **2017**, *56*, 12–24. [CrossRef]
126. Melini, F.; Melini, V.; Luziatelli, F.; Ficca, A.G.; Ruzzi, M. Health-Promoting Components in Fermented Foods: An Up-to-Date Systematic Review. *Nutrients* **2019**, *11*, 1189. [CrossRef]
127. Christensen, L.F.; García-Béjar, B.; Bang-Berthelsen, C.H.; Hansen, E.B. Extracellular microbial proteases with specificity for plant proteins in food fermentation. *Int. J. Food Microbiol.* **2022**, *381*, 109889. [CrossRef]
128. Ji, D.; Ma, J.; Xu, M.; Agyei, D. Cell-envelope proteinases from lactic acid bacteria: Biochemical features and biotechnological applications. *Compr. Rev. Food Sci. Food Saf.* **2021**, *20*, 369–400. [CrossRef]
129. Siezen, R.J. Multi-domain, cell-envelope proteinases of lactic acid bacteria. In *Lactic Acid Bacteria: Genetics, Metabolism and Applications*; Konings, W.N., Kuipers, O.P., In't Veld, J.H.J.H., Eds.; Springer: Dordrecht, The Netherlands, 1999; pp. 139–155. [CrossRef]
130. Kieliszek, M.; Pobiega, K.; Piwowarek, K.; Kot, A.M. Characteristics of the proteolytic enzymes produced by lactic acid bacteria. *Molecules* **2021**, *26*, 1858. [CrossRef]
131. Liu, M.; Bayjanov, J.R.; Renckens, B.; Nauta, A.; Siezen, R.J. The proteolytic system of lactic acid bacteria revisited: A genomic comparison. *BMC Genom.* **2010**, *11*, 36. [CrossRef]
132. Melville, P.A.; Benites, N.R.; Ruz-Peres, M.; Yokoya, E. Proteinase and phospholipase activities and development at different temperatures of yeasts isolated from bovine milk. *Res. J. Dairy Sci.* **2011**, *78*, 385–390. [CrossRef] [PubMed]
133. Klein, N.; Zourari, A.; Lortal, S. Peptidase activity of four yeast species frequently encountered in dairy products—Comparison with several dairy bacteria. *Int. Dairy J.* **2002**, *12*, 853–861. [CrossRef]
134. Fan, M.; Guo, T.; Li, W.; Chen, J.; Li, F.; Wang, C.; Shi, Y.; Li, D.X.; Zhang, S. Isolation and identification of novel casein-derived bioactive peptides and potential functions in fermented casein with *Lactobacillus helveticus*. *Food Sci. Hum. Wellness* **2019**, *8*, 156–176. [CrossRef]
135. Carrasco-Castilla, J.; Hernández-Álvarez, A.J.; Jiménez-Martínez, C.; Gutiérrez-López, G.F.; Dávila-Ortiz, G. Use of proteomics and peptidomics methods in food bioactive peptide science and engineering. *Food Eng. Rev.* **2012**, *4*, 224–243. [CrossRef]
136. Macwan, S.R.; Dabhi, B.K.; Parmar, K.D. Aparnathi Whey and its Utilization. *Int. J. Curr. Microbiol. App. Sci.* **2016**, *5*, 134–155. [CrossRef]
137. Alves, M.P.; Moreira, R.O.; Júnior, P.H.R.; Martins, M.C.F.; Perrone, I.T.; Carvalho, A.F. Soro de leite: Tecnologias para o processamento de coprodutos. *Rev. Do Inst. Laticínios Cândido Tostes* **2014**, *69*, 212–226. [CrossRef]

138. Batista, M.A.; Campos, N.C.A.; Silvestre, M.P.C. Whey and protein derivatives: Applications in food products development, technological properties and functional effects on child health. *Cogent Food Agric.* **2018**, *4*, 1509687. [CrossRef]
139. Smithers, G.W. Whey and whey proteins—From 'gutter-to-gold'. *Int. Dairy J.* **2008**, *18*, 695–704. [CrossRef]
140. Smithers, G.W. Whey-ing up the options—Yesterday, today and tomorrow. *Int. Dairy J.* **2015**, *48*, 2–14. [CrossRef]
141. Khan, U.M.; Selamoglu, Z. Nutritional and medical perspectives of whey protein: A historical overview. *J. Pharm. Care* **2019**, *7*, 112–117. [CrossRef]
142. Aslam, M.Z.; Firdos, S.; Li, Z.; Wang, X.; Liu, Y.; Qin, X.; Yang, S.; Ma, Y.; Xia, X.; Zhang, B.; et al. Detecting the Mechanism of Action of Antimicrobial Peptides by Using Microscopic Detection Techniques. *Foods* **2022**, *11*, 2809. [CrossRef] [PubMed]
143. Mehra, R.; Kumar, H.; Kumar, N.; Ranvir, S.; Jana, A.; Buttar, H.S.; Telessy, I.G.; Awuchi, C.G.; Okpala, C.O.R.; Korzeniowska, M.; et al. Whey proteins processing and emergent derivatives: An insight perspective from constituents, bioactivities, functionalities to therapeutic applications. *J. Funct. Foods* **2021**, *87*, 104760. [CrossRef]
144. Zhao, C.; Chen, N.; Ashaolu, T.J. Whey proteins and peptides in health-promoting functions–A review. *Int. Dairy J.* **2022**, *126*, 105269. [CrossRef]
145. Chavan, R.S.; Shradda, R.; Kumar, A.; Nalawade, T. Whey based beverage: Its functionality, formulations, health benefits and applications. *J. Food Process. Technol.* **2015**, *6*. [CrossRef]
146. Zotta, T.; Solieri, L.; Iacumin, L.; Picozzi, C.; Gullo, M. Valorization of cheese whey using microbial fermentations. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 2749–2764. [CrossRef]
147. Singh, A.R.; Pathak, S.; Mitra, A.; Verma, M.; Banga, A. Dairy Processing Waste Valorization and Utilization: A Review. *IJARESM* **2021**, *9*, 780–783.
148. Bandara, T.A.; Munasinghe-Arachchige, S.P.; Gamlath, C.J. Fermented whey beverages: A review of process fundamentals, recent developments and nutritional potential. *Int. J. Dairy Technol.* **2023**, *76*, 737–757. [CrossRef]
149. Shukla, M.; Jha, Y.K.; Admassu, S. Development of probiotic beverage from whey and pineapple juice. *J. Food Process. Technol.* **2013**, *4*, 1000206. [CrossRef]
150. Sasi Kumar, R. Development, quality evaluation and shelf life studies of probiotic beverages using whey and Aloe vera juice. *J. Food Process. Technol.* **2015**, *6*, 486. [CrossRef]
151. Faisal, S.; Chakraborty, S.; Devi, W.E.; Hazarika, M.K.; Puranik, V. Sensory evaluation of probiotic whey beverages formulated from orange powder and flavor using fuzzy logic. *Int. Food Res J.* **2017**, *24*, 703–710.
152. Rosa, L.S.; Santos, M.L.; Abreu, J.P.; Rocha, R.S.; Esmerino, E.A.; Freitas, M.Q.; Mársico, E.T.; Campelo, P.H.; Pimentel, T.C.; Silva, M.C.; et al. Probiotic fermented whey-milk beverages: Effect of different probiotic strains on the physicochemical characteristics, biological activity, and bioactive peptides. *Int. Food Res.* **2023**, *164*, 112396. [CrossRef] [PubMed]
153. Quintieri, L.; Fanelli, F.; Monaci, L.; Fusco, V. Milk and its derivatives as sources of components and microorganisms with health-promoting properties: Probiotics and bioactive peptides. *Foods* **2024**, *13*, 601. [CrossRef]
154. Liutkevičius, A.; Speičienė, V.; Kaminskas, A.; Jablonskienė, V.; Alenčikienė, G.; Mieželienė, A.; Bagdonaitė, L.; Vitkus, D.; Garmienė, G. Development of a functional whey beverage, containing calcium, vitamin D, and prebiotic dietary fiber, and its influence on human health. *CyTA-J. Food* **2016**, *14*, 309–316. [CrossRef]
155. Moreno-Montoro, M.; Olalla-Herrera, M.; Rufián-Henares, J.Á.; Martínez, R.G.; Miralles, B.; Bergillos, T.; Navarro-Alarcón, M.; Jauregi, P. Antioxidant, ACE-inhibitory and antimicrobial activity of fermented goat milk: Activity and physicochemical property relationship of the peptide components. *Food Funct.* **2017**, *8*, 2783–2791. [CrossRef]
156. Silva e Alves, A.T.; Spadoti, L.M.; Zacarchenco, P.B.; Trento, F.K. Probiotic functional carbonated whey beverages: Development and quality evaluation. *Beverages* **2018**, *4*, 49. [CrossRef]
157. Turkmen, N.; Akal, C.; Özer, B. Probiotic dairy-based beverages: A review. *J. Funct. Foods* **2019**, *53*, 62–75. [CrossRef]
158. Skryplonek, K.; Dmytrów, I.; Mituniewicz-Małek, A. Probiotic fermented beverages based on acid whey. *JDS* **2019**, *102*, 7773–7780. [CrossRef]
159. Gulec, H.A.; Cinar, K.; Bagci, U.; Bagci, P.O. Production of concentrated whey beverage by osmotic membrane distillation: Comparative evaluation of feed effect on process efficiency and product quality. *Int. Dairy J.* **2021**, *121*, 105115. [CrossRef]
160. Karabegović, I.; Stamenković, S.S.; Lazić, M.; Đorđević, N.; Danilović, B. Antimicrobial activity and overall sensory acceptance of fermented goat whey beverage: Process conditions optimization using response surface approach. *Adv. Technol.* **2022**, *11*, 26–35. [CrossRef]
161. Naik, B.; Kohli, D.; Walter, N.; Gupta, A.K.; Mishra, S.; Khan, J.M.; Joakim Saris, P.E.; Irfan, M.; Rustagi, S.; Kumar, V. Whey-carrot based functional beverage: Development and storage study. *J. King Saud Univ. Sci.* **2023**, *35*, 102775. [CrossRef]
162. Vargas-Díaz, S.; Ciro-Velasquez, H.J.; Sepúlveda-Valencia, J.U. Development and characterization of a fermented dairy beverage from permeated and concentrated sweet whey sweetened with tagatose. *RFNAM* **2023**, *76*, 10201–10212. [CrossRef]
163. Hernández, T.; Vélez-Ruiz, J.F. Development, characterization, and stability of a functional beverage from whey. *MOJ Food Process Technols.* **2024**, *12*, 140–147. [CrossRef]

164. Vélez, N.; Argel, A.; Kissmann, A.K.; Alpízar-Pedraza, D.; Escandón, P.; Rosenau, F.; Ständker, L.; Firacative, C. Pore-forming peptide C14R exhibits potent antifungal activity against clinical isolates of *Candida albicans* and *Candida auris*. *Front. Cell. Infect. Microbiol.* **2024**, *14*, 1389020. [CrossRef] [PubMed]
165. Panghal, A.; Patidar, R.; Jaglan, S.; Chhikara, N.; Khatkar, S.K.; Gat, Y.; Sindhu, N. Whey valorization: Current options and future scenario—A critical review. *Nutr. Food Sci.* **2018**, *48*, 520–535. [CrossRef]
166. Sharma, V.; Singh, A.; Thakur, M. Valorization of Whey in Manufacturing of Functional Beverages: A Dairy Industry Perspective. In *Whey Valorization: Innovations, Technological Advancements and Sustainable Exploitation*; Springer: Singapore, 2023; pp. 355–369. [CrossRef]
167. Abish, Z.A.; Alibekov, R.S.; Tarapoulouzi, M.; Bakhtybekova, A.R.; Kobzhasarova, Z.I. Review in deep processing of whey. *Cogent Food Agric.* **2024**, *10*, 2415380. [CrossRef]
168. Brandenburg, K.; Heinbockel, L.; Correa, W.; Lohner, K. Peptides with dual mode of action: Killing bacteria and preventing endotoxin-induced sepsis. *BBA-Biomembr.* **2016**, *1858*, 971–979. [CrossRef]
169. Fernandes, A.; Jobby, R. Bacteriocins from lactic acid bacteria and their potential clinical applications. *Appl. Biochem. Biotechnol.* **2022**, *194*, 4377–4399. [CrossRef]
170. Bakare, O.O.; Gokul, A.; Niekerk, L.A.; Aina, O.; Abiona, A.; Barker, A.M.; Basson, G.; Nkomo, M.; Otomo, L.; Keyster, M.; et al. Recent Progress in the Characterization, Synthesis, Delivery Procedures, Treatment Strategies, and Precision of Antimicrobial Peptides. *Int. J. Mol. Sci.* **2023**, *24*, 11864. [CrossRef]
171. Mehraj, I.; Hamid, A.; Gani, U.; Iralu, N.; Manzoor, T.; Saleem Bhat, S. Combating antimicrobial resistance by employing antimicrobial peptides: Immunomodulators and therapeutic agents against infectious diseases. *ACS Appl. Bio Mater.* **2024**, *7*, 2023–2035. [CrossRef]
172. Strempel, N.; Strehmel, J.; Overhage, J. Potential application of antimicrobial peptides in the treatment of bacterial biofilm infections. *Curr. Pharm. Des.* **2015**, *21*, 67–84. [CrossRef]
173. Newstead, L.L.; Varjonen, K.; Nuttall, T.; Paterson, G.K. Staphylococcal-produced bacteriocins and antimicrobial peptides: Their potential as alternative treatments for *Staphylococcus aureus* infections. *Antibiotics* **2020**, *9*, 40. [CrossRef] [PubMed]
174. Pang, X.; Song, X.; Chen, M.; Tian, S.; Lu, Z.; Sun, J.; Li, X.; Lu, Y.; Yuk, H.G. Combating biofilms of foodborne pathogens with bacteriocins by lactic acid bacteria in the food industry. *Compr. Rev. Food Sci. Food Saf.* **2022**, *21*, 1657–1676. [CrossRef]
175. Nowicka, J.; Janczura, A.; Pajączkowska, M.; Chodaczek, G.; Szymczyk-Ziółkowska, P.; Walczuk, U.; Gościniak, G. Effect of camel peptide on the biofilm of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* formed on orthopedic implants. *Antibiotics* **2023**, *12*, 1671. [CrossRef]
176. Chen, X.; Yang, J.; Qu, C.; Zhang, Q.; Sun, S.; Liu, L. Anti-Staphylococcus aureus effects of natural antimicrobial peptides and the underlying mechanisms. *Future Microbiol.* **2024**, *19*, 355–372. [CrossRef]
177. Huang, M.B.; Brena, D.; Wu, J.Y.; Shelton, M.; Bond, V.C. SMR peptide antagonizes *Staphylococcus aureus* biofilm formation. *Microbiol. Spectr.* **2024**, *12*, e02583-23. [CrossRef]
178. Daba, G.M.; Elkhateeb, W.A. Ribosomally synthesized bacteriocins of lactic acid bacteria: Simplicity yet having wide potentials–A review. *Int. J. Biol. Macromol.* **2024**, *256*, 128325. [CrossRef]
179. Sadanov, A.K.; Saubenova, M.G.; Oleinikova, E.A.; Aitzhanova, A.A.; Baimakhanova, B.B. Population-Resistant Consortium of Lactic Acid Bacteria Lactobacillus delbrueckii 5, Lactobacillus gallinarum 1, Lactobacillus paracasei 33-4, Lactobacillus parabuchneri 3, acetic acid bacteria Acetobacter syzygii 2 and yeast Kluyveromyces marxianus 19 with High Antagonistic Activity Against a Wide Range of Yeasts of the Genus Candida—Causative Agents of Candidiasis of Various Localizations, Mold Fungi Isolated from the Human Intestinal Tract in Dysbacteriosis, as well as the Most Common Representatives of Opportunistic Bacteria. Patent No. 35266 KZ, 10 July 2020. (In Russian)
180. Sadanov, A.K.; Saubenova, M.G.; Oleinikova, E.A.; Aitzhanova, A.A. Consortium of Lactic Acid Bacteria Lactobacillus fermentum A15, Lactobacillus paracasei 4m-2b, Acetic Acid Bacteria Acetobacter fabarum 4-4M and lactose-fermenting yeast Kluyveromyces marxianus 4MA, antagonistically Active Against Fungal and Bacterial Microorganisms, Intended for Fermentation of Milk Whey. Patent No. 35463 KZ, 14 August 2020. (In Russian)
181. Aitzhanova, A.; Oleinikova, Y.; Mounier, J.; Hymery, N.; Leyva Salas, M.; Amangeldi, A.; Saubenova, M.; Alimzhanova, M.; Ashimuly, K.; Sadanov, A. Dairy associations for the targeted control of opportunistic Candida. *World J. Microbiol. Biotechno.* **2021**, *37*, 143. [CrossRef]
182. Oleinikova, Y.; Alybayeva, A.; Daugaliyeva, S.; Alimzhanova, M.; Ashimuly, K.; Yermekbay, Z.; Khadzhibayeva, I.; Saubenova, M. Development of an antagonistic active beverage based on a starter including *Acetobacter* and assessment of its volatile profile. *Int. Dairy J.* **2024**, *148*, 105789. [CrossRef]
183. Sadanov, A.K.; Saubenova, M.G.; Oleinikova, E.A.; Aitzhanova, A.A.; Baimakhanova, B.B. Method for Preparing a Functional Fermented Milk Drink Based on Whey. Patent No. 35394 KZ, 10 July 2020. (In Russian)
184. Sadanov, A.K.; Saubenova, M.G.; Oleinikova, E.A.; Aitzhanova, A.A. Method for Producing a Synbiotic Drink Based on Milk Whey. Patent No. 35461 KZ, 14 August 2020. (In Russian)

185. Oleinikova, Y.; Amangeldi, A.; Aitzhanova, A.; Saubenova, M.; Yelubaeva, M. Influence of dairy microorganisms and their consortia on indigenous microflora. *Int. J. Eng. Res. Appl.* **2019**, *9*, 46–49. Available online: https://www.ijera.com/papers/vol9no7/Series-5/F0907054649.pdf (accessed on 10 December 2024).
186. Chizhayeva, A.; Oleinikova, Y.; Saubenova, M.; Sadanov, A.; Amangeldi, A.; Aitzhanova, A.; Alybaeva, A.; Yelubaeva, M. Impact of probiotics and their metabolites in enhancement the functional properties of whey-based beverages. *AIMS Agric. Food* **2020**, *5*, 521–542. [CrossRef]
187. Oleinikova, Y.; Amangeldi, A.; Yelubaeva, M.; Alybaeva, A.; Amankeldy, S.; Saubenova, M.; Chizhaeva, A.; Aitzhanova, A.; Berzhanova, R. Immobilization effects of wheat bran on enhanced viability of dairy starters under acid and bile salts stresses. *Appl. Food Biotechnol.* **2020**, *7*, 215–223. [CrossRef]
188. Ji, S.; An, F.; Zhang, T.; Lou, M.; Guo, J.; Liu, K.; Zhu, Y.; Wu, J.; Wu, R. Antimicrobial peptides: An alternative to traditional antibiotics. *Eur. J. Med. Chem.* **2023**, *265*, 116072. [CrossRef] [PubMed]
189. Sukmarini, L.; Atikana, A.; Hertiani, T. Antibiofilm activity of marine microbial natural products: Potential peptide-and polyketide-derived molecules from marine microbes toward targeting biofilm-forming pathogens. *J. Nat. Med.* **2024**, *78*, 1–20. [CrossRef] [PubMed]
190. Goel, N.; Fatima, S.W.; Kumar, S.; Sinha, R.; Khare, S.K. Antimicrobial resistance in biofilms: Exploring marine actinobacteria as a potential source of antibiotics and biofilm inhibitors. *Biotechnol. Rep.* **2021**, *30*, e00613. [CrossRef]
191. Davoudi, M.; Gavlighi, H.A.; Javanmardi, F.; Benjakul, S.; Nikoo, M. Antimicrobial peptides derived from food byproducts: Sources, production, purification, applications, and challenges. *Compr. Rev. Food Sci. Food Saf.* **2024**, *23*, e13422. [CrossRef]
192. Arasu, M.V.; Al-Dhabi, N.A. Antibacterial activity of peptides and bio-safety evaluation: In vitro and in vivo studies against bacterial and fungal pathogens. *J. Infect. Public Health* **2023**, *16*, 2031–2037. [CrossRef]
193. Wang, X.; Yang, X.; Wang, Q.; Meng, D. Unnatural amino acids: Promising implications for the development of new antimicrobial peptides. *Crit. Rev. Microbiol.* **2023**, *49*, 231–255. [CrossRef]
194. Erdem Büyükkiraz, M.; Kesmen, Z. Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds. *J. Appl. Microbiol.* **2022**, *132*, 1573–1596. [CrossRef]
195. Zhang, F.; Yang, P.; Mao, W.; Zhong, C.; Zhang, J.; Chang, L.; Wu, X.; Liu, H.; Zhang, Y.; Gou, S.; et al. Short, mirror-symmetric antimicrobial peptides centered on "RRR" have broad-spectrum antibacterial activity with low drug resistance and toxicity. *Acta Biomater.* **2022**, *154*, 145–167. [CrossRef]
196. Sowers, A.; Wang, G.; Xing, M.; Li, B. Advances in Antimicrobial Peptide Discovery via Machine Learning and Delivery via Nanotechnology. *Microorganisms* **2023**, *11*, 1129. [CrossRef]
197. Almaaytah, A. Antimicrobial peptides as potential therapeutics: Advantages, challenges and recent advances. *Farmacia* **2022**, *70*, 991–1003. [CrossRef]
198. Dullius, A.; Goettert, M.I.; de Souza, C.F.V. Whey protein hydrolysates as a source of bioactive peptides for functional foods–Biotechnological facilitation of industrial scale-up. *J. Funct. Foods* **2018**, *42*, 58–74. [CrossRef]
199. Purohit, K.; Reddy, N.; Sunna, A. Exploring the potential of bioactive peptides: From natural sources to therapeutics. *Int. J. Mol. Sci.* **2024**, *25*, 1391. [CrossRef] [PubMed]
200. Barati, M.; Javanmardi, F.; Mousavi Jazayeri, S.M.H.; Jabbari, M.; Rahmani, J.; Barati, F.; Nickho, H.; Davoodi, S.H.; Mousavi Khaneghah, A. Techniques, perspectives, and challenges of bioactive peptide generation: A comprehensive systematic review. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 1488–1520. [CrossRef]
201. Tsai, C.T.; Lin, C.W.; Ye, G.L.; Wu, S.C.; Yao, P.; Lin, C.T.; Wan, L.; Tsai, H.H.G. Accelerating antimicrobial peptide discovery for who priority pathogens through predictive and interpretable machine learning models. *ACS Omega* **2024**, *9*, 9357–9374. [CrossRef]
202. Martínez-Culebras, P.V.; Gandía, M.; Garrigues, S.; Marcos, J.F.; Manzanares, P. Antifungal peptides and proteins to control toxigenic fungi and mycotoxin biosynthesis. *Int. J. Mol. Sci.* **2021**, *22*, 13261. [CrossRef]
203. Corrêa, J.A.F.; de Melo Nazareth, T.; Rocha, G.F.D.; Luciano, F.B. Bioactive antimicrobial peptides from food proteins: Perspectives and challenges for controlling foodborne pathogens. *Pathogens* **2023**, *12*, 477. [CrossRef]
204. Ahmed, T.A.; Hammami, R. Recent insights into structure–function relationships of antimicrobial peptides. *J. Food Biochem.* **2019**, *43*, e12546. [CrossRef]
205. Grassi, L.; Maisetta, G.; Esin, S.; Batoni, G. Combination strategies to enhance the efficacy of antimicrobial peptides against bacterial biofilms. *Front. Microbiol.* **2017**, *8*, 2409. [CrossRef]
206. Aransiola, S.A.; Selvaraj, B.; Maddela, N.R. Bacterial biofilm formation and anti-biofilm strategies. *Res. Microbiol.* **2024**, *175*, 104172. [CrossRef]
207. Juszczuk-Kubiak, E. Molecular aspects of the functioning of pathogenic bacteria biofilm based on *Quorum Sensing* (QS) signal-response system and innovative non-antibiotic strategies for their elimination. *Int. J. Mol. Sci.* **2024**, *25*, 2655. [CrossRef] [PubMed]
208. Hussaini, I.M.; Oyewole, O.A.; Sulaiman, M.A.; Dabban, A.I.; Sulaiman, A.N.; Tarek, R. Microbial anti-biofilms: Types and mechanism of action. *Res. Microbiol.* **2024**, *175*, 104111. [CrossRef] [PubMed]

209. Manobala, T. Peptide-based strategies for overcoming biofilm-associated infections: A comprehensive review. *Crit. Rev. Microbiol.* **2024**, 1–18. [CrossRef] [PubMed]
210. Perfect, J.R. The antifungal pipeline: A reality check. *Nat. Rev. Drug Discov.* **2017**, *16*, 603–616. [CrossRef]